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A.M.A. JOURNAL OF

DISEASES OF CHILDREN

PART I

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Joanne Whitaker, Robert H. Page, Cyril S. Stulberg, and Wolf W. Zuelzer

Phallic Urethra in Female Pseudohermaphroditism
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Skin pH Pattern in the Newborn Infant
Hans Behrendt and Marvin Green

Conversion Hysteria in Childhood
Alanson Hinman

Congenital Stenosis of the Aortic and Pulmonary Valvular Areas of the Heart
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Histiocytoma of the Bronchus
Talcott Bates and Osman H. Hull

Chronic Vitamin A Intoxication
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Gargoylism
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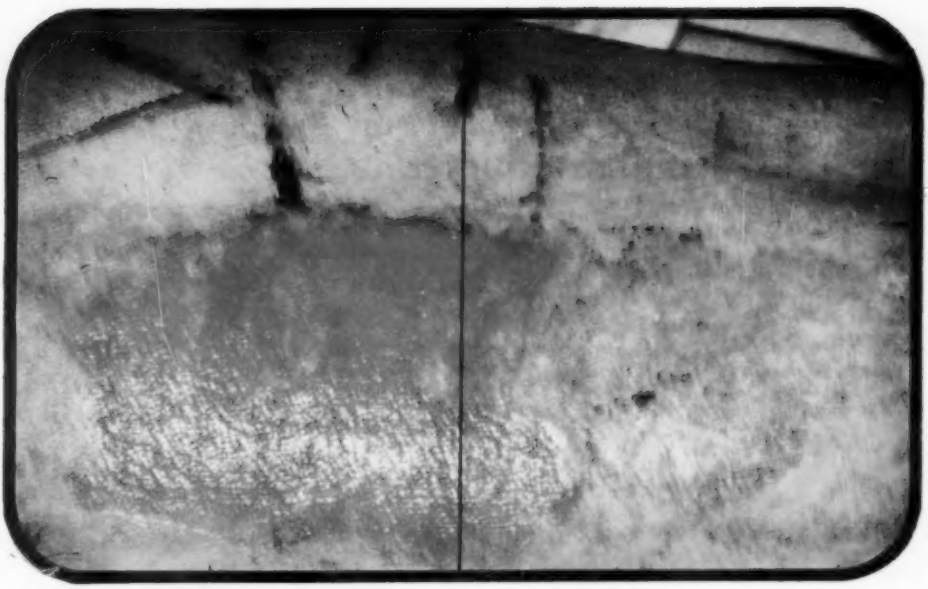

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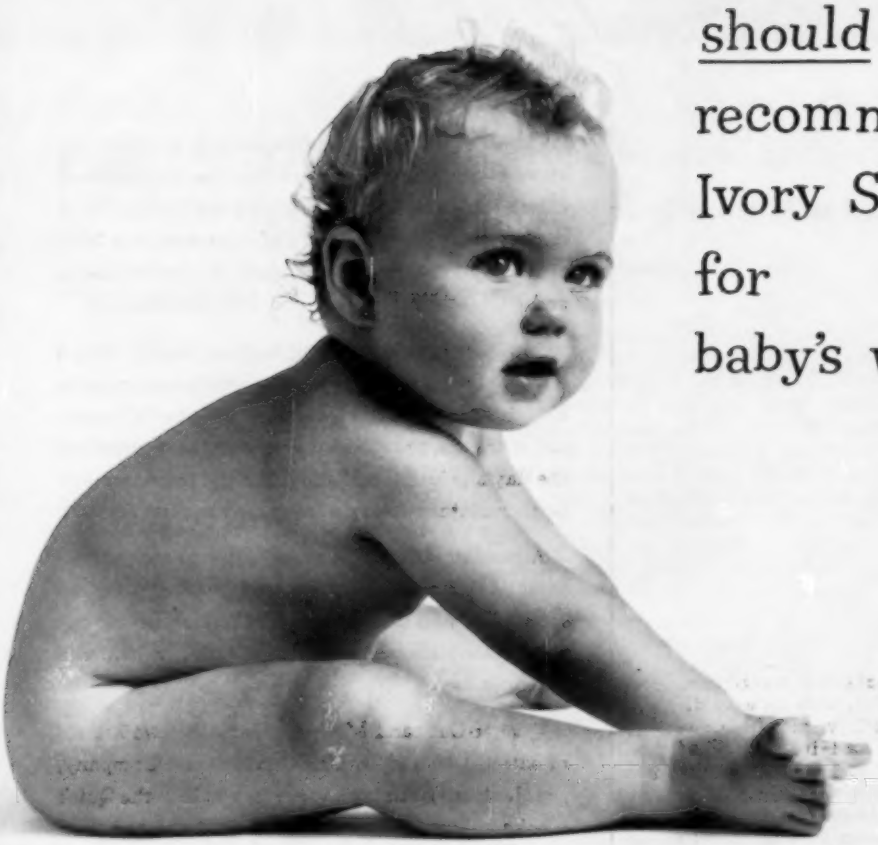

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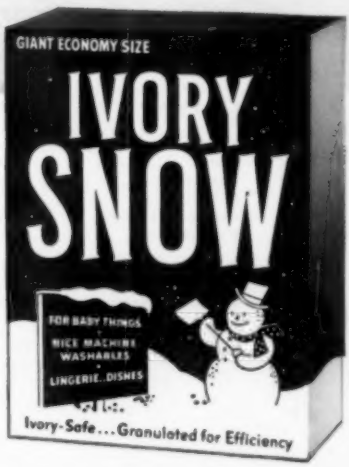

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Rapid Identification of Enteropathogenic Escherichia Coli O127:B_8 by the Fluorescent Antibody Technique

JOANNE WHITAKER, M.D.; ROBERT H. PAGE, M.S.; CYRIL S. STULBERG, Ph.D., and WOLF W. ZUELZER, M.D., Detroit

The existence of a large number of serologically distinct types of Escherichia coli and the pathogenic significance of a number of these strains in the causation of both epidemic and sporadic diarrheas of infants are well recognized. The rapid detection and identification of enteropathogenic E. coli strains has become a necessity for epidemiologic and clinical control of infantile diarrheal disease. Conventional bacteriologic and serologic methods usually require at least 24 to 48 hours. The fluorescent antibody technique, by which a large number of different micro-organisms and viruses have already been identified,[1-11] seemed especially applicable to the problem of pathogenic E. coli. This paper describes the application of the fluorescent antibody method as a diagnostic test for identification of E. coli O127:B_8, which can be carried out within 15 to 25 minutes directly from stool specimens or rectal swabs.

Materials and Methods

An epidemic of diarrhea in 1954 in the premature nursery of The Children's Hospital was extensively studied by Stulberg et al.[12] and was shown to be caused by enteropathogenic E. coli O127:B_8. At the time of the epidemic, rectal swabs and stool specimens had been obtained systematically and cultural and serological identification of the organisms had been made. Duplicate stool specimens taken on the same day as the culture had been stored at −20 C for future reference. These specimens made it possible three years later to restudy the bacteriological aspects of the epidemic with the fluorescent antibody technique and to evaluate the reliability of this method for the rapid identification of the infecting organisms in the stools.

The following materials were examined: (*a*) the original stored frozen stool specimens; (*b*) cultures made from thawed aliquots of the specimens; when growth was obtained, the organisms were identified by specific agglutination (OB rabbit antiserum specific for enteropathogenic E. coli O127:B_8); (*c*) rectal swabs from patients currently in the hospital with diarrheal disease.

The readings of results obtained by the fluorescent antibody technique were recorded without knowledge of the results obtained on the comparable stool specimens and swabs in 1954 or of the results of the standard bacteriologic methods currently used on duplicate specimens.

1. *Preparation of Fluorchroming Reagent.*—Rabbit antisera (OB) specific for enteropathogenic E. coli O127:B_8 and for O125:B_{15}, for control purposes, were prepared as previously described by Stulberg et al.[12] The agglutinating titers were 1:1280.

The globulin portion of the rabbit antisera was fractionated by salting out with 17.5% sodium sulfate over a 24-hour period. The precipitates were dissolved in a small amount of distilled water and dialyzed against distilled H_2O and isotonic saline.

The globulin fraction was coupled to fluorscein isocyanate by the Coons technique.[10]

From the Child Research Center of Michigan.

Received for publication Sept. 5, 1957; accepted Sept. 26.

Supported in part by Public Health Service Grants H-3119 and E-859.

The coupled material was sterilized by use of an HA Millipore filter and stored in the dark at 4 C in 2 ml. quantities in sterile rubber-capped vials. The final agglutinating OB antibody titer after coupling was 1:80.

2. Preparation of Slides for Examination.—(*a*) Stool Specimens: A pinpoint quantity of frozen stool specimen was placed in a sterile test tube and mixed with 1 ml. of sterile saline. One drop of the stool suspension was placed on a slide, air-dried, and fixed by heating. One drop of labeled antiserum was placed on the slide. In order to be certain that optimal staining resulted, these slides were stained for 45 minutes. To prevent evaporation the slides were covered with a Petri dish lined with filter paper moistened with isotonic saline. After staining they were washed for five minutes with isotonic saline. The excess fluid was removed by briefly draining and wiping with bibulous paper. The slides were mounted with 10% glycerin phosphate buffered saline under a cover slip and sealed with paraffin.

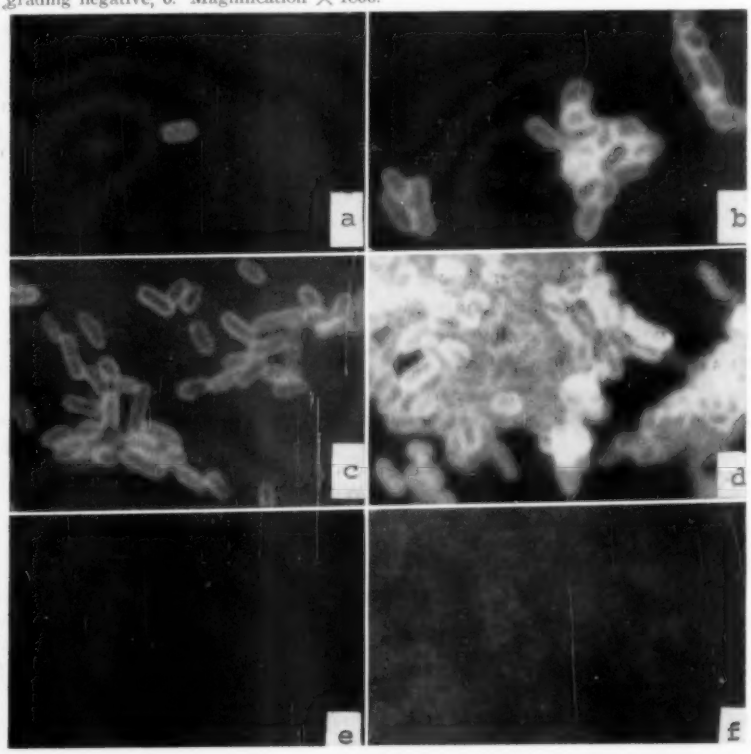
(*b*) Bacterial Smears: Smears of bacteria were prepared by taking a small colony of bacteria from the culture medium and mixing it on a slide with a drop of sterile saline. The slides were air-dried and heat-fixed, and one drop of labeled reagent was applied. The bacteria were stained for 15 minutes and washed with saline for 5 minutes.

(*c*) Rectal Swabs: The swabs were moistened with a small amount of sterile saline and directly smeared on the slide. These smears were then prepared like those of the bacterial smears (*b*).

3. Fluorescent Microscopy and Photography.—The Reichert microscope with a high-pressure 200-watt mercury vapor arc light source and suitable filters was used to examine the slides. Photographs were taken with Kodak Tri-X Film with exposures ranging from two to five minutes.

All O127:B_8 bacteria stained with a specific labeled antiserum gave the same intense brilliant "street light" green fluorescence. In specimens reported as positive the outline of the capsule had to be distinctly identified. Negative fluorescence

Fig. 1.—Identification of E. coli O127:B_8 by fluorescent antibody technique of rectal swabs and stool specimens. (*a* to *d*) Varying numbers of fluorescent O127:B_8 organisms after exposure to conjugated homologous antiserum, grading positive 1+ to 4+; (*a*) and (*b*) from rectal swabs currently obtained; (*c*) and (*d*) from stool specimens from the 1954 epidemic. (*e* to *f*) Cross reacting nonpathogenic E. coli exposed to O125:B_{18} conjugated antiserum, showing varying faint fluorescence and indistinguishable capsules—negative fluorescent reaction, grading negative, 0. Magnification × 1800.



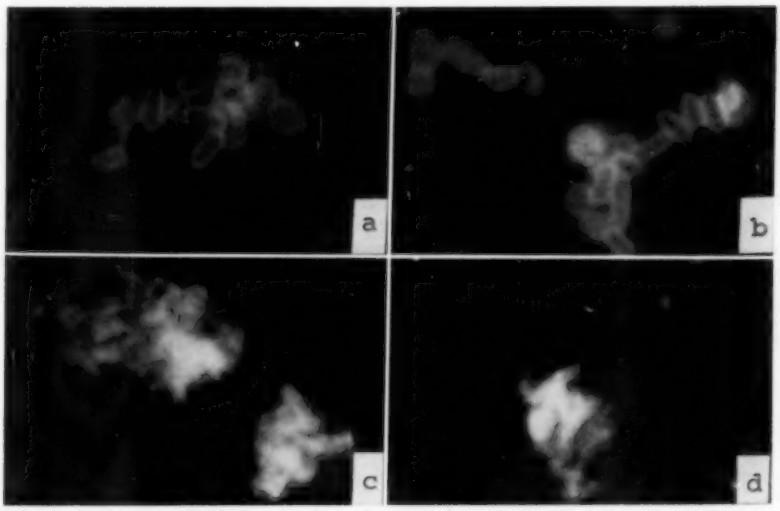


Fig. 2.—Fluorescent O127:B_8 organisms from stool specimen after three days of neomycin therapy. Four fields of the same slide are illustrated: (*a*) distinct fluorescent capsules; (*b*) faint and rounded fluorescent capsules; (*c* to *d*) fluorescent masses of dead organisms and fragmented bacteria. Magnification × 1800.

was reported when no fluorescent capsules could be seen.

In order to estimate the number of bacteria present, an arbitrary system of grading was established as illustrated in Figure 1. This grading correlated moderately well with the amount of cultural growth.

Grade	Fluorescent Organisms
4+	Slide covered with fluorescent organisms in massive clumps
3+	Moderate number of fluorescent clumps and single organisms
2+	Many single organisms and a few clumps
1+	Single organisms and/or occasional clumps
0	Negative—no single organism identified

Frequently, in cases in which the patient had been receiving neomycin therapy at the time the specimen was taken, clumps of fluorescent material were seen which most likely represented masses of dead bacteria. Unless single organisms could be identified, however, these masses were reported as negative (Fig. 2, *c* and *d*).

Results

1. *Specificity of Labeled Antibody* (Table 1). The labeled antibodies prepared against enteropathogenic E. coli O127:B_8 and against O125:B_{15} were found to stain specifically the corresponding homologous bacteria. The enteropathogenic E. coli O127:B_8 antibody did not strain O125:B_{15} organisms, and vice versa (Fig. 3). Neither antibody stained any of six additional serotypes of enteropathogenic E. coli (O26:B_6, O55:B_5, O86:B_7, O111:B_4, O119:B_{14}, and O126:B_{16}) nor any of six other bacterial species (Staphylococcus, Streptococcus, Pseudomonas, E. freundii, Shigella, and nonpathogenic E. coli). Enteropathogenic E. coli O127:B_8 organisms exposed to specific but unlabeled antibody showed no fluorescence.

TABLE 1.—*Specificity of Fluorescent Antibodies*

Antigen Tested	Antiserum	Fluorescence
Enteropathogenic E. coli	Labeled Antiserum	
O127:B_8	O127:B_8	Pos.
O127:B_8	O125:B_{15}	Neg.
O125:B_{15}	O125:B_{15}	Pos.
O125:B_{15}	O127:B_8	Neg.
O26:B_6	O127:B_8	Neg.
O55:B_5	O127:B_8	Neg.
O86:B_7	O127:B_8	Neg.
O111:B_4	O127:B_8	Neg.
O119:B_{14}	O127:B_8	Neg.
O126:B_{16}	O127:B_8	Neg.
Other bacteria		
Staphylococcus	O127:B_8	Neg.
Streptococcus	O127:B_8	Neg.
Pseudomonas	O127:B_8	Neg.
E. freundii	O127:B_8	Neg.
Shigella	O127:B_8	Neg.
Nonpathogenic E. coli	O127:B_8	Neg.
	Unlabeled Antiserum	
O127:B_8	O127:B_8	Neg.

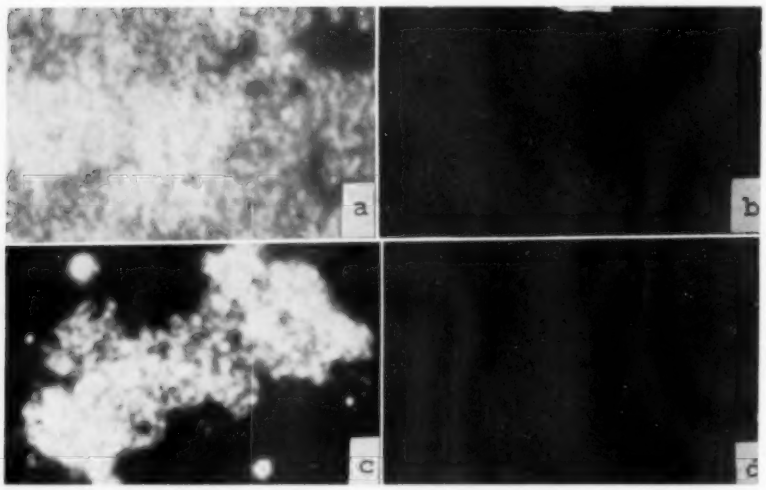


Fig. 3.—Control studies to demonstrate negative fluorescent reaction with conjugated heterologous serum. (*a*) O125:B_{15} bacteria exposed to O127:B_8-conjugated antiserum. Photographed with visible light to demonstrate presence of bacteria. (*b*) Same field as (*a*) but with blue-violet filter in place—no fluorescence. (*c*) O127:B_8 bacteria exposed to O125:B_{15}-conjugated antiserum. Photographed in the same manner as (*a*). (*d*) Same field as (*c*) but photographed with blue-violet filter in place—no fluorescence. Magnification × 1800.

Suspensions of rectal swabs from 20 patients currently under observation with diarrhea not due to enteropathogenic E. coli O127:B_8 which on culture had yielded no enteropathogenic E. coli showed no fluorescent organisms.

Rectal swabs taken from three patients currently hospitalized for diarrhea were identified by the fluorescent antibody technique as containing enteropathogenic E. coli O127:B_8, and this was subsequently confirmed by the cultural and agglutination method (Fig. 1, *a* and *b*).

It has been observed that weak cross-reactions between specific antiserum and certain enteropathogenic E. coli organisms may occur in agglutination tests.[14] In such instances lack of specific agglutination can be demonstrated by heating the cross reacting bacteria. Although such nonspecific agglutination was not encountered in this study, it was desirable to see whether such reactions would occur with the fluorescent antibody technique. Since O127:B_8 antiserum did not cause nonspecific slide agglutination, three instances of nonspecific agglutination which had occurred with O125:B_{15} antiserum were checked for fluorescent cross reactions. In each case the fluorescence was so weak and the capsular outline so indistinct that either they were read as negative by the above criteria or, in any case, they were readily distinguishable from the positive reaction (Fig. 1, *e* and *f*). In no case was such "cross reaction" by the fluorescent method encountered when the labeled enteropathogenic E. coli O127:B_8 antiserum was used. This problem will be further investigated and reported in a later paper.

2. *Sensitivity.*—From the premature infants originally studied in the 1954 epidemic, 128 stool specimens were examined by the fluorescent antibody technique. The original collection had been carried out randomly throughout the patients' hospital stay, and the specimens represented infants in various stages of incubation, acute illness, and convalescence and before, during, and after antibiotic (neomycin) therapy. For 114 specimens simultaneous rectal swab cultures had been made in 1954. No comparable

rectal swabs had been obtained for the other 14 of the 128 stool specimens.

All of the stool specimens corresponding to the 53 rectal swab cultures found positive in 1954 for enteropathogenic E. coli O127:B_8 gave positive results with the fluorescent antibody method. While there was thus 100% correlation with originally positive cases, 39 additional positive results were obtained by the fluorescent method on testing the remaining 61 specimens from cases originally reported as negative by rectal swab cultures in 1954. In each of these cases the infant had at one time received neomycin therapy and enteropathogenic E. coli organisms had been identified in the stool, either previously or subsequently, by the conventional methods. In view of the specificity of the method as described above, the positive fluorescence in these 39 cases would therefore seem to indicate that with this technique organisms could be recognized which no longer had viability or were at least incapable of reproduction, so that the cultural method failed to detect them.

That this interpretation of positive fluorescence as staining of nonreproductive bacteria is correct is further demonstrated by a comparison of the results obtained with the stored stool specimens by the cultural method and by the fluorescent technique. Of the total of 128 stored stool specimens only 24 yielded growth of E. coli O127:B_8 on culturing the thawed stools after three years of storage, whereas 97 positive identifications from the same specimens were made with the fluorescent antibody technique.

To illustrate this point further, the findings in a selected group of cases in the 1954 epidemic are presented in Figure 4. It will be noted that each of the patients represented in this graph had positive cultures for enteropathogenic E. coli O127:B_8 during his hospitalization. In Case 1, in which a reference specimen was obtained at a time when the patient had both diarrhea and a positive culture, the specimen was positive by the fluorescent method. The patient at the time had been placed on neomycin therapy, and seven days later (at which t[illegible] therapy had already been dis-

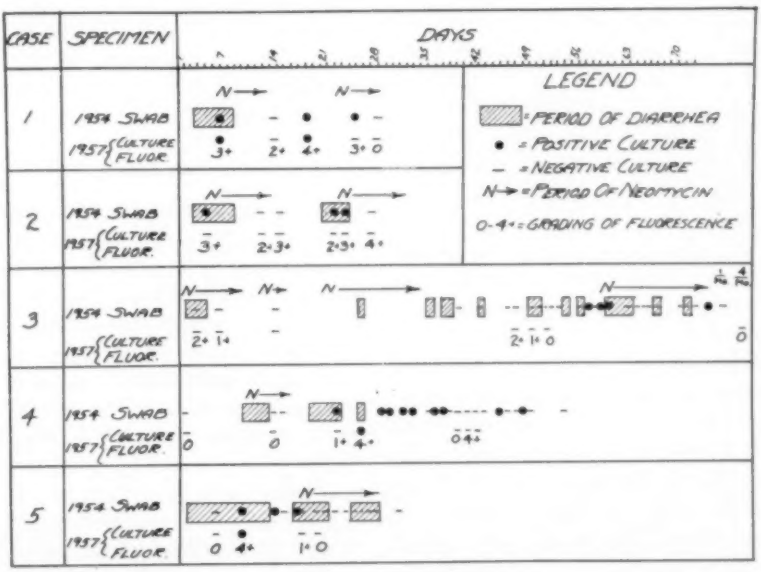


Fig. 4.—Course of the disease and identification of the infecting agent by various methods for five patients in the 1954 epidemic.

TABLE 2.—*Comparison of Fluorescent Antibody Technique with Bacteriologic-Serologic Cultures for Identification of E. Coli O127:B₈*

Specimens	Total No.	Fluorescent Technique (Thawed Stools, 1957)		Original Bacteriologic-Serologic Cultures (Swabs, 1954)		Bacteriologic-Serologic Cultures (Thawed Stools, 1957)	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
Stools with comparable swab cultures		19		19		19	
		34		34			34
		39			39		39
		3			3	3	
			19		19		19
Stools and swabs, No.	114	95	19	53	61	22	92
Stools for which no comparable swab culture data were available		1				1	
		1					1
			11				11
			1			1	
Stools, No.	14	2	12			2	12
Total	128	97	31	53	61	24	104

continued) the stool culture had been negative but the corresponding reference specimen could now be shown to be positive. Within five days the conventional culture had again become positive and another culture one week later was still positive. Both the corresponding reference specimens were also positive. The apparent bacteriological relapse as judged by the results of the cultural method was in reality continuous excretion of organisms as shown by the fluorescent tests. These observations confirm the validity and the greater sensitivity of the fluorescent method. At the same time, they furnish an explanation for the observation, made in many cases in the 1954 epidemic, that patients whose stools had been repeatedly found "negative" in the wake of short-term neomycin therapy subsequently again showed growth of enteropathogenic E. coli O127:B_8. Cases 2, 4, and 5 illustrate essentially the same pattern. Case 3 demonstrates that positive findings could be obtained by the fluorescent technique long before there was sufficient growth to permit identification by the conventional method.

As compared with the 95 positive fluorescent results, cultural growth of enteropathogenic E. coli O127:B_8 was obtained from only 22 of the 114 stored stool specimens for which comparable rectal swabs had been cultured in 1954. In each of these the fluorescence was also positive. In three cases both methods gave positive results even though the corresponding rectal swab culture in 1954 had been negative, indicating in retrospect failure of the rectal swab method of culture. All of the 19 fluorescent-negative stool specimens corresponded to negative rectal swab cultures reported in 1954.

Additional stool specimens from the 1954 epidemic were examined for which no corresponding rectal swab specimens had been obtained at the time. In this group of 14 there were 2 positive specimens by the fluorescent method, one with a negative culture and one with a positive culture. There was one positive culture with negative fluorescence, the sole failure of the fluorescent method in the entire study. The remaining 11 specimens gave negative results by both methods.

Comment

The advantages of the fluorescent method are obvious. Not only is it far more rapid than conventional identification by culture and agglutination but it permits the detection of organisms which, presumably as the result of antibiotic therapy, are no longer capable of reproduction and therefore of being demonstrated by the cultural method. Since pathogenic strains of E. coli cannot be differentiated from nonpathogenic strains on morphologic grounds alone, the advantage of demonstrating the serotype in the absence of growth is considerable. From an epidemiological point of view this is an important point where patients have already

been placed on therapy at the time when bacteriologic examination is made. The method otherwise offers a convenient and rapid technique for serial follow-up studies on patients excreting organisms.

The sensitivity of the method has been shown to be greater than that of the conventional methods. Its full range has not yet been explored. It should be possible to demonstrate by specific fluorescence small numbers of organisms in cases in which the pathogenic types represent only a small portion of the organisms in the stool. Such colonies of enteropathogenic E. coli, as for instance in carriers, are apt to be missed when colonies are selected for subculturing and agglutination tests but may be picked up by the more sensitive fluorescent antibody technique.

The preparation of the labeled antibody apart, the technique is simple and practical. The specificity of the reagent prepared by us was such that identification as well as exclusion could be made. In view of the total number of serotypes of E. coli now known or supposed to be pathogenic, pooled reagents for screening purposes would appear practical. At present a polyvalent antiserum for the identification of 10 different known enteropathogenic strains of E. coli is being prepared for screening a large number of diarrheal stool specimens.

Summary

This paper describes the application of the fluorescent antibody technique to the identification of pathogenic serotypes of Escherichia coli. Stored frozen material from an epidemic of enteropathogenic E. coli O127:B_8 diarrhea in 1954, extensively studied by conventional methods, permitted a thorough evaluation of the specificity and sensitivity of the fluorescent antibody method. The technique has a high degree of specificity and is more sensitive and more rapid than identification by culture and specific agglutination. It is able to identify organisms which have lost the power of reproduction or are present in such small numbers that they escape detection in the mixed stool flora. The fluorescent method can be used directly with specimens of stool or rectal swabs.

A restudy of an epidemic of diarrhea caused by an enteropathogenic strain of E. coli provides new insight into therapeutic effects and epidemiologic patterns.

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Phallic Urethra in Female Pseudohermaphroditism

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The presence of a urethra coursing through the phallus would seem to be evidence of maleness. However, certain female patients with intersexual external genitalia (female pseudohermaphrodites) have been observed either with a single urethra running through the clitoris or with this, plus a second urethra, emptying into the urogenital sinus. Recently, five cases of phallic urethra have been observed and the findings of one other unreported case has been studied. These will be presented and discussed in detail in order to point out the factors involved in differential diagnosis.

The study of intersexuality would be more rewarding if it could be approached from an etiological standpoint. In any given case, however, exact etiologic factors cannot always be determined, but if consideration is given to each of the possible causes (developmental anomaly, fetal adrenal hyperplasia, and exogenous androgens) a reasonable basis can be constructed for diagnosis and treatment.

Theoretically, intersexuality with a phallic urethra can occur in one of three ways: (1) by anomalous development, in which normal sequences of differentiation are blighted during early fetal life so that a combination of gross genital abnormalities occurs, among which may be a phallic urethra; (2) by fetal adrenal hyperactivity, in which the male components of the female external genitalia are stimulated to development; the most extreme degree of this adrenal masculinization results in closure of the urogenital sinus and the formation of a clitoral urethra; (3) by maternal androgenic influence, which results in fetal masculinization analogous to the feminization that is seen with hypospadias; this maternal influence can be either endogenous (arrhenoblastoma) or exogenous (administered testosterone or, possibly, progesterone). Androgenic stimulation during fetal life which causes intersexuality has been well demonstrated by the animal experiments of Burns [1] on the opossum, by van Wagenen and Hamilton [2] on monkeys, and by Jost [3] on rabbits, as well as by other workers.

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Phallic Urethra as Developmental Anomaly

Two types of anomalous development which result in a phallic urethra have been observed: Type 1, the so-called vaginal urethra group, and Type 2, a group associated with mixed anomalies.

Phallic Urethra as a Congenital Anomaly, Type 1

We have reported this type previously,[4] in which an apparent arrest occurs just at the time of formation of the phallic tubercle, so that formation of the urethral plate is unimpeded. The resultant anomalies are limited to the phallus, urogenital sinus, and uterus; they are remarkably constant and consist of both phallic and vaginal urethrae and bifid Müllerian structures. In addition to the two cases reported previously,[4] data have been received on an additional one (Figs. 1A and 1B).

CASE 1.—A girl was noted to have a phallic urethra, through which a ureteral catheter could be passed and through which the child voided part of her urine, and a vaginal urethra, into which a urethral sound could be passed. The phallic

Fig. 1A (Case 1).—External genitalia of female pseudohermaphrodite, vaginal urethral type; a catheter is in the phallic urethra and a metal sound is in the true urethra. (Made available by Dr. H. A. Buchtel.)

Fig. 1B (Case 1).—Lateral radiograph of same case. (Made available by Dr. H. A. Buchtel.)

Fig. 2A (Case 2).—Phallus with external urethral meatus on tip of glans. Note imperforate anus.

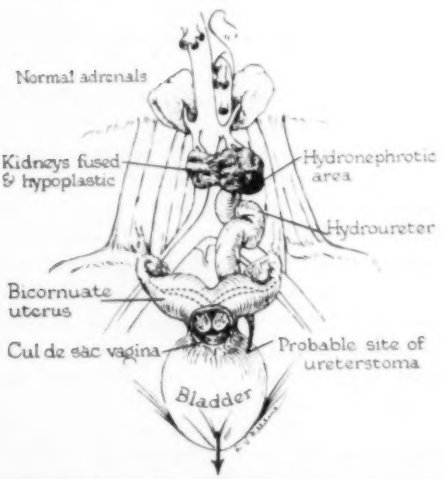

Fig. 2B (Case 2).—Hypoplastic kidney in pelvic area, normal adrenals, bicornuate uterus, tubes, ovaries.

urethra was closed surgically. Subsequently, two transvaginourethral resections of the bladder neck were performed for relief of obstruction.

Phallic Urethra as a Congenital Anomaly, Type 2

Case 2.—A white infant, shown in Figures 2A, 2B, and 2C, entered the hospital at the age of 12 hours because of cyanosis and imperforate anus and for sex determination. The infant's mother had had an unremarkable pregnancy, uncomplicated by illness or drug therapy. The delivery was normal and at full term; the infant weighed 4 lb. 3 oz. at birth. There were two normal siblings. The infant had numerous congenital anomalies in addition to the unaccountable cyanosis seen at birth. The imperforate anus required immediate attention. The external genitalia were not definitely classifiable: Urine and meconium spurted from the external urinary meatus in the phallic glans (Fig. 2A). The phallus had slight chordee and a small prepuce. The rudimentary scrotum was bifid, and no testes were palpable. A raphe extended from the glans to the rectal dimple. A distance of 3.5 cm. separated the terminal colon from the perineal dimple. Additional anomalies were a congenital web neck, shortened right leg with underdeveloped

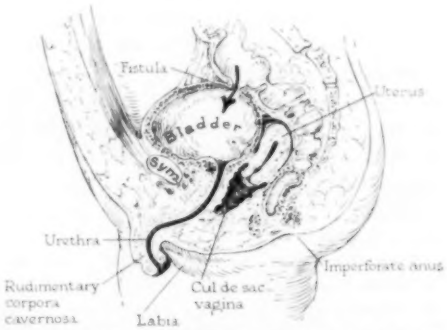

Fig. 2C (Case 2).—Illustration of phallus with urethra. Vesicocolic fistula and female internal genitalia.

muscles, clubfoot, and a large umbilical hernia with diastasis recti.

Sigmoid perineal colostomy and cystostomy were easily performed under general anesthesia. A vesicocolic fistula and female internal genitalia with bicornuate uterus and possible pyosalpinx were noted at the time of operation. The child became very cyanotic and died nine hours postoperatively. At autopsy the following additional findings were made (Figs. 2B and 2C): The child had normal ovaries; no testes were found. She was, therefore, a female pseudohermaphrodite. The phallus was a clitoris and contained a urethra and cavernous bodies. The vagina was blind and did not connect with the urethra. The uterus was bicornuate. The kidneys were small, rested in the midline retroperitoneal area of the pelvis, and were hypoplastic. The left one had only a few functional glomeruli. The adrenals were normal. There was a patent foramen ovale. The skin sex chromatin was female.

During life the infant had presented a difficult problem of sex determination on the basis of examination of the external genitalia alone. The configuration suggested maleness, but the absence of testes and the smallness of the phallus cast doubt upon this supposition. The female characteristics were found only by a combined laparotomy and autopsy; there was no opportunity during life to do hormone or sex chromatin determinations. The associated multiple anomalies have been reported in this type of pseudohermaphroditism—especially the double uterus, imperforate anus, hypoplastic kidneys, and some of the skeletal anomalies.

CASE 3.*—An infant was admitted to the University of California Hospital at the age of 2 months for sex determination because of imperforate anus with discharge of feces per vagina, maldevelopment of heart, and underdevelopment. The infant was the product of the mother's only pregnancy. Family history and this pregnancy were normal except for the mother's excessive weight gain. Delivery was uneventful, and the baby's length and weight were normal. There was some intermittent acrocyanosis and, occasionally, difficult breathing through the nose. Weight was excessive.

At the age of 2 months the child was 52 cm. long and weighed 3950 gm. A loud blowing systolic murmur over the precordium was of maximum intensity at the second to third left intercostal space. The heart size was normal by physical and roentgenographic examinations, but an interventricular septal defect or pulmonic stenosis was suspected. There were some inguinal lymph nodes and a small umbilical hernia. Feces passed from a fistulous tract posterior to the vaginal orifice but not from the usual location of the anus. No dimple was noted. Urine flowed mainly from the normally placed urethral meatus (vaginal) and the vagina-rectum (cloaca-like) and also from the glans of the phallus. The median raphe extended along the phallus. The labia minora were underdeveloped and partly fused. The hypertrophic phallus (2 cm. long) had a foreskin and a glans with an external urethral meatus on its tip. No testes were palpable.

Routine blood studies and urinalysis were normal. Skin sex chromatin pattern was female. No hormonal tests were done. Cystoscopic examination was done by S. Olsen, M.D. A catheter traversed the phallic urethra; the cystoscope in the anterior of two openings ("vaginal" urethra) of the "vagina" entered the bladder, which appeared normal. The catheter in the phallic urethra could be seen to pass into the bladder. No cervix was then seen, owing to inability to inspect the posterior of the two orifices of the "vagina." However, there was no direct communication between the phallic urethra and the "vagina." At another time, a retrograde pyelogram revealed a bladder situated slightly high; the right kidney was situated abnormally low, possibly malrotated, with a possible double pelvis. The left kidney was small but normally placed. There was no evidence of actual renal-function deficiency. Previously, an intravenous urogram had not been very helpful. A vaginogram was necessary and demonstrated that the child had a normal apical concavity, with a uterine cervix outlined in relief but without connection with the phallic urethra.

At the age of 2 years 10 months, the clitoris was possibly slightly smaller. There was no evidence of urinary infection or clinical heart-function deficiency, and the patient's physical and mental development were normal. Consideration is being given to the repair of the rectovaginal fistula and anus to be done before she is 5 or 6 years old, then to the scrotal fusion, vagina, and the removal of the phallus.

This patient is a female with phallic urethra, female sex chromatin, and associated anomalies of heart, rectum, and undescended kidney—nonadrenal in cause but probably due to blighted development.

Phallic Urethra Secondary to Fetal Adrenal Hyperplasia (So-Called Adrenogenital Syndrome)

In pseudohermaphroditism due to congenital adrenal hyperplasia the specific enzyme which normally enables the metabolic change of cholesterol-progesterone to cortisone is absent; the cortisone deficiency

* Case 3 was made available by W. C. Deamer, M.D.

Fig. 3A (Case 4).—Prepuce with moderate chordee.

causes an endogenous corticotropin discharge, with the result that increased amounts of adrenal androgens are formed. These can be measured in the urine as 17-ketosteroids or, with even more specificity, as pregnanetriol. The androgens, acting through fetal life, masculinize the female genitalia. The most extreme alteration, called Type V by Prader,[5] consists of an enclosed urogenital sinus with the urethra continuing to the end of the clitoris. An instance of a slightly less extreme type, approaching Type IV of Prader, is reported here.

CASE 4.—Figures 3A and 3B show a white infant who entered the hospital at the age of 9 days because of an enlarged clitoris and possible adrenal crisis. The mother had had no other pregnancies. A maternal first cousin was reported to have had a large clitoris, which was operated upon; the cousin is now well at 5 years of age.

A large clitoris was noted at birth in this patient. Vomiting started at the age of 7 days, and when it became serious an adrenal crisis was suspected.

Physical examination on hospital admission revealed a small, immature child who was dehydrated but in no great distress. The patient's temperature remained subnormal through the hospitalization. The clitoris was 1.5 cm. long and had moderate chordee (Fig. 3A). The prepuce continued into the labia minora. The urethra opened on the ventral surface of glans clitoris in a manner similar to a first-degree hypospadias. No vagina was seen. The labia majora were large, rugous, and not fused. No testes were palpable.

A chemical analysis of the blood showed the typical changes of hypoadrenocorticism with hyperkalemia. Despite replacement therapy and hydrocortisone administration, the patient died 13 days after birth.

At autopsy the adrenals were found to be grossly enlarged (Fig. 3B): One weighed 6.5 gm., and the other, 6.0 gm. Hemorrhage was present. The internal genitalia consisted of a small vagina (2×2 cm.), ovaries, tubes, and a single uterus. The vagina had a pinpoint outlet (1 mm. in diameter) into the posterior urethra, which continued externally in the clitoris for two-thirds of its length and then consisted mainly of a trough extending to a glans clitoris. The labia minora were very rudimentary. The sex chromatin was female in the skin, vaginal mucosa, and blood cells.

This infant was a classic example of female pseudohermaphroditism resulting from adrenal cortical hyperplasia, accompanied by evidences of the lack of the salt-and-water-controlling hormone, which produced an Addisonian crisis. Again, a phallic urethra made sex determination clinically difficult. Death resulted from adrenal insufficiency.

In 1934 a similar patient was studied by one of us (W. A. R.)[6,7]; this patient

Fig. 3B (Case 4).—Enlarged adrenals, uterus, tubes, and ovaries and external genitalia with enlarged phallus. (Made available by Col. E. Edwards [MC].)

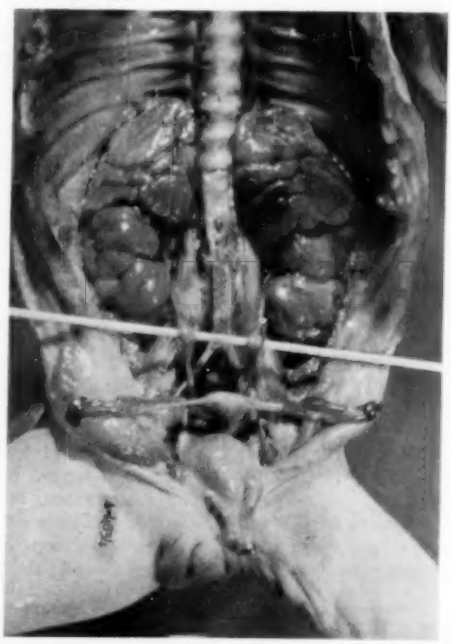

Fig. 4. (Case 5).—Enlargement of phallus. External urethral meatus opened midway in ventral surface of phallus. (Made available by Col. W. E. Edwards [MC].)

showed precocious growth at 15 months of age and developed a phallus containing a urethral opening at the tip of the glans. There was no evidence of adrenal cortical insufficiency. An orchiopexy was attempted, but no testes were found. The patient died the following day. Hormonal assays and sex chromatin studies had not yet been developed. At autopsy greatly enlarged adrenals, a small vagina, cervix, uterus, tubes, and normal ovaries were found. A phallic urethra was present, into which the urogenital sinus opened. In 1956, the sex chromatin was found to be female.

Case 5.—Figure 4 illustrates a third case, with less extensive development of the phallic portion of the urethra. This white infant entered the hospital at the age of 10 months for treatment of pseudohermaphroditic features noted at birth. No anomalies were present in the family. The child was delivered normally at full term and weighed 6 lb. at birth. No neonatal difficulties were noted.

A small "penis" with moderate curvature was noted, and an external urethral meatus opened midway on its ventral surface. A median raphe extended from the glans to the anus, and rugous empty scrotal sacs were present. No testes were palpated. The clitoris measured 3.5 cm. in length and 2.8 cm. in circumference. Rectal palpation did not reveal prostatic tissue.

The child was well developed and slightly obese. Measurements for height and skull development were in the 75th percentile, and weight was in the 90th percentile. At 13 months of age the patient's epiphyseal age was between 18 and 24 months. The opinion was that the "penis" was a clitoris with a prepuce and contained a urethra coursing to its midlength. It was thought that the meatal opening might be a urogenital sinus and that the "scrota" were fused labia majora. Cystoscopic examination confirmed the presence of a urethra in the clitoris and revealed a fairly normal vagina and cervix. The vagina connected with the midurethra. The sex chromatin pattern was female in the skin and buccal mucosa. The blood eosinophils were 195 and 215 per cubic millimeter. Basal 17-hydroxycorticoids were 1.9 to 2.5 mg/24 hours (normal), and rose to 4.1 mg. after 20 units of corticotropin (ACTH) was given intravenously. Basal 17-ketosteroids were 6.9 to 8.1 mg/24 hours (normal, 0 to 0.5 mg.) and rose to 10.0 mg., indicating adrenal hyperplasia. On a regimen of 25 mg. of cortisone daily the 17-ketosteroids fell to 2.3 mg/24 hours.

At birth the phallus had a ventral urethral opening in the middle of the shaft. The testes were not palpable, and no urogenital sinus was visible externally. Accordingly, the sex was difficult to determine on physical examination alone. The cystoscopic visualization of the cervix during hospitalization suggested that this was a gonadal female, although an ovarian biopsy was not performed. The finding of elevated urinary 17-ketosteroids and their subsequent suppression by cortisone proved that adrenal cortical overactivity was the causative factor. In such a case laparotomy for gonadal biopsy was not necessary.

Phallic Urethra from Maternal Androgens

Excess androgens during fetal life may be produced by other sources than the fetal adrenal gland. Arrhenoblastomas have caused intersexuality,[8,9] and androgen administered experimentally to pregnant animals [1-3] and to humans [2,4] has resulted in masculinization of the female fetus. The following case which was studied here, may be another example.

Case 6.—Figure 5 [10] shows a white child who entered the hospital at the age of 6 months because of pseudohermaphroditic features first noted at birth. The infant was regarded as a boy by his parents. There were no known familial anomalies or diseases. The child's mother had had no previous pregnancies. Testosterone had been administered to the mother because of nausea and vomiting (30 mg. daily) starting about the 7th week of

Fig. 5 (Case 6).—External urethral meatus on gland on enlarged phallus. (Made available by E. Grunwaldt and T. Bates.[10])

pregnancy and continued for 51 days (a total of about 1730 mg.). Her voice deepened; the hormone was stopped. She was delivered of a normal full-term infant weighing 7 lb. 9 oz. Oxygen was administered to the infant for treatment of extrasystoles and cyanosis during the first day. At birth it was thought that the "penis" was quite small, and urine could be seen passing through a small meatus on the top of the glans.

The child appeared physically and mentally normal at the time of hospital admission. Weight, height, and skull circumference were at the 75th percentile, and no other anomalies were detected. The external genitalia had a median raphe from the anus to a frenulum, which, in turn, led to a foreskin. The slightly rugous scrotum was only half the normal size, and no testes could be palpated. The phallus was 6 mm. in diameter and 20 mm. long. Erectile tissue, resembling corpora cavernosa, was palpable. The prepuce, when retracted, seemed adherent to a small external urethral meatus, from which urine was forcibly discharged by the patient. No other openings were present. Rectal examination did not reveal a prostate gland, but it was the opinion of several observers that a small uterus was palpable.

The 17-ketosteroids were normal (0.3 mg/24 hours). The epiphyseal age was equivalent to the chronological age. The intravenous pyelograms revealed no adrenal abnormality. Biopsy of the skin showed a female chromosomal sex pattern. A dorsal slit of prepuce exposed the external urethral meatus, into which a catheter could be inserted for only a short distance. Roentgenograms showed a urogenital sinus, normal bladder, and vagina.

At laparotomy the adrenals were found to be of normal size. Tubes, ovaries, and a uterus were seen in the pelvis; no testes were found. A biopsy from the superior and inferior poles of each ovary revealed numerous primordial follicles. No testicular cells or their embryological equivalents were encountered.

The determination of this patient's sex was difficult. There was no external urogenital sinus, but a cystogram revealed a a vagina and cervix. The sex chromatin pattern was female, and the laparotomy confirmed the presence of female gonads. The normal 17-ketosteroid excretion was evidence against fetal adrenal overactivity. However, since testosterone had been given to the mother in sufficient amounts to deepen her voice, we suspect that this was the cause of the intersexual development of the fetus.

Diagnostic Tests

Since one of the main problems in pseudohermaphroditism is determination of the true sex of the infant as exactly as possible, particularly to relieve family anxiety and for future healthy emotional development of the child, the following tests are used by us at present (Table).

1. Chromosome analysis can be done on practically any tissue. During life it is perhaps best done on scrapings of the buccal mucosa.

After the mucosa is cleared of mucus with the edge of a glass slide or tongue blade, another slide is used to scrape the mucous membrane. The cells are then smeared onto a third slide, which is placed at once in Davidson's solution. The slides are stained by the Papanicolaou or the Feulgen procedure. Chromatin clumps (XX chromosome) are found at the edge of the nucleus in the female, and it is characteristic that 80% of the cells have such clumps at the periphery of nucleus; 20% or less is characteristic of the male. Between these two figures, the smear is not adequate for diagnosis.

2. Hormone assays: Urinary 17-ketosteroids are elevated with adrenal cortical hyperplasia and are decreased by cortisone

Tests for Differential Diagnosis of Pseudohermaphroditism

	Physical Examination	Chromosome Analysis	Hormone Tests *	Urethrocystograms & Vaginograms	Bone Age	Cortisone Therapy	Surgical Exploration
Congenital anomaly	Abnormal phallus; other anomalies: imperforate anus, duplication, urinary tract, other systems	Either male or female	17-K, N; FSH, N	Bicornuate uterus, other anomalies	Normal	No effect	Gonads and internal genitalia of either sex; other anomalies
Female pseudohermaphrodite, usually with adrenal hyperplasia	Enlarged clitoris, urogenital sinus; often palpable uterus	Female	17-K, elevated; FSH, N or low	Small uterus & cervix	Advanced	Reduces 17-K; reverses masculinization	Normal female gonads and internal genitalia
Male pseudohermaphrodite	Hypospadias to female external genitalia; vaginal size proportional to degree of hypospadias; usually palpable prostate	Male	17-K, N; FSH, N or high	No uterus or cervix	Normal or retarded	No effect	Inadequately developed male gonads and internal genitalia

*17-K, 17-ketosteroids; FSH, follicle-stimulating hormone; N, normal.

therapy. A 24-hour urine specimen is preserved with 15 cc. of concentrated hydrochloric acid. Normal values lie near 0 in children up to 8 years of age, rising to 1.5 to 5.0 mg. before puberty, then to adult values of 15 (± 5) mg/24 hours in males and 10 (± 5) in females. If levels greater than 2.5 mg. are found shortly after birth, adrenal overactivity is present. If adrenal tumor is present, the β fraction of total neutral 17-ketosteroids will be elevated from the normal level of 10 to 30% to a level exceeding 50%.

Follicle-stimulating hormone (FSH) is elevated in gonadal deficiency and decreased in primary pituitary deficiency. Immature mice are injected with preparations from the 24-hour urine specimen. The test in children is less valuable than in adults, since the normal levels are seldom much above zero before puberty. The adult values are above 5 and below 50 mouse units per 24 hours.

3. Urethrocystograms and vaginograms are more useful for research and treatment than for practical use in diagnosis. Injections of air into the bladder and dye into the vagina give the best differentiation. Vaginal abnormalities (duplication, for example) may thus be detected, since these are due to anomalous development, not to hormonal action.

4. Intravenous urograms and presacral gas insufflation are seldom necessary in adrenal hyperplasia unless a tumor is suspected. Urinary tract anomalies which would be demonstrated by intravenous urography are often associated with anomalies of the genital tract.

5. Epiphyseal (bone) age is increased in adrenal hyperplasia but not in other disorders related to intersexuality.

6. A therapeutic trial with cortisone is given for adrenal hyperplasia with dosage of 12.5 mg. of cortisone t. i. d. or 5 mg. of prednisone (Meticorten) b. i. d. A reduction of the 17-ketosteroids to normal levels indicates adrenal overactivity.

7. Surgical exploration is rarely or never necessary in adrenal cortical hyperplasia, since the therapeutic test proves that the adrenal cortices are hyperplastic. In other forms of female intersexuality it is often necessary to determine the exact status of the internal genitalia in order to plan subsequent plastic surgical treatment.

8. Blood chemical determinations of sodium, potassium, chloride, and carbon dioxide are desirable to uncover a latent Addisonism, or preoperatively, or when infection is present.

Previously Reported Cases

In addition to the 6 new cases reported in this article, 20 other cases of phallic urethra are known to us; 9 of the total of 26 patients were observed in our clinic.

The first recorded case of phallic urethra was that of Clarke,[11] in England, in 1892; the first American publication was that of Atkinson and Mason.[12] Of the 20 cases, adrenal hyperplasia was proved in 12 [6,7,13-21,23,28] and no adrenal influence was demonstrable in 8 cases.[4,11,12,22-24,26] In the latter, the cause was probably a developmental anomaly, genetic conditioning, or maternal androgens. Of recorded cases in which there was a hypertrophic clitoris without a phallic urethra but with a vaginal urethra there were approximately 200 or more associated with adrenal hyperplasia and about 15 without adrenal hyperplasia.

There are five reported cases of arrhenoblastoma,[8,9,25] in which, by the increased production of androgen, the fetuses were influenced as follows: Two developed female pseudohermaphroditism [8,9] (large clitoris without urethra, and virilization; an autopsy performed on one of these infants showed female internal genitalia); the third fetus was aborted; the other two infants were boys, presumably normal.[25]

Hayles et al.[24] reported a girl with the urethra at the base of her large phallus, possibly as a result of methyltestosterone Linguets administered to the mother during pregnancy. The mother ingested 10 to 20 mg. daily, but irregularly, for alopecia from the beginning of the third month to the end of the ninth month, for a total dose of 1.5 gm. The infant, examined at 7 months, had a chordee, empty rugous scrota, female sex chromatin, and grossly normal female internal genitalia. There are two reports of perineal urethra in female pseudohermaphrodites who were born of mothers who were treated with androgenic hormones.[24]

Progesterone given to pregnant females in order to prevent miscarriage has been attended by evidences of masculinization in the offspring; obstetricians and endocrinologists have described occasional cases to us. This hormone has a metabolic action like that of androgens.

In the following abstract of such a case made available by M. Grossman, M.D.) [27] the mother had previously had five miscarriages and had given birth to two live infants.

During the 18th week of the mother's eighth pregnancy, therapy of 120 mg. daily of progesterone orally (Lutocylol) was begun; this dose was increased to 240 mg. at the 28th week until delivery, and occasionally 320 mg. daily may have been taken. The total dose was large. She was delivered of an 1815 gm. girl during the 34th week. The only abnormality detected was an enlarged clitoris, without a urethra; the labia were enlarged; otherwise the external genitalia were those of a normal girl. After the third day of life the clitoris started to decrease in size, and it was continuing to do so at the last examination, at about 2 years of age. At one month of age (length 46 cm.) chronologically—38 weeks since conception—urinary 17-ketosteroids were 0.55 mg/24 hours (normal) and epiphyseal age was less than 35 weeks. The baby thrived and developed normally.

If sufficient progesterone is taken early enough in human pregnancy (probably before the 10th to 11th week) it could, we think, induce phallic urethra and female pseudohermaphroditism. Grossman's case could probably have been such a case, if progesterone was started just at the time of formation of the phallic tubercle. Since it was started later (at the 18th week), the normal Müllerian structure, vaginal urethra, and normal clitoris were already formed properly. Masculinization resulted only in the growth of clitoris and labia, and it was too late for a phallic urethra to have developed.

Summary

The presence of a urethra coursing in a phallus when the remainder of the external genitalia are equivocal for sex determination poses a difficult diagnostic problem. The findings in 6 female pseudohermaphrodite children (5 were previously unreported) are described, and the 20 previously reported cases of phallic urethra in female pseudohermaphrodites are noted.

The etiology may be a blight which results in a true congenital anomaly. This may be an arrest about the time of formation of the phallic tubercle (so-called vaginal urethra type) or a major fetal disaster, result-

ing in a gross anomaly which includes the external genitalia (three cases).

A second cause of phallic urethra may be congenital adrenal hyperplasia (two cases). A third cause, similar in mechanism, may be intersexual development from maternal androgens (one case).

Chromosome analysis, hormone assays, urethrograms and vaginograms, urograms, gas insufflation, determination of bone age, therapeutic cortisone trial, and even surgical exploration may be necessary to arrive at a definitive diagnosis.

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Pneumocystis Pneumonia

Report of a Case

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Pneumocystis carinii pneumonia or interstitial plasma-cell pneumonia is a common infection in Europe, where it occurs endemically or in small institutional epidemics. It affects chiefly premature or otherwise debilitated infants with a peak incidence at the age from 6 weeks to 4 months, but the disease has also been encountered in three adults.[1] In this country three instances have thus far been recorded,[2,3] and five other cases have been seen in Canada.[4,5] Two further patients have recently been reported from Australia.[6] These cases all occurred in infants and were recognized only at autopsy. Two other reports describe three patients with interstitial plasma-cell pneumonia, one seen in this country[7] and the other two in Canada.[8] In the former no mention is made of Pneumocystis organisms, while in the latter the agent could not be found. The European literature indicates that the clinical syndrome of this disease is sufficiently characteristic to suggest the diagnosis. The duration is said to be between four and six weeks, but considerable variations have been observed. At present, no practical laboratory test is available and no effective therapy has been found, although all antibiotic and chemotherapeutic agents have been tried. The mortality is said to range between 20% and 25%. The findings at autopsy show a widespread pulmonary consolidation with large intra-alveolar masses of a minute organism, tentatively identified as Pneumocystis carinii, which some regard as a protozoon, others, as a fungus. It is doubtful if the agent has been isolated in culture or if the infection has been transmitted to experimental animals. A detailed review of Pneumocystis pneumonia including a discussion of the controversy regarding the nature of the agent and the results of animal experiments has appeared recently in the American literature.[9] The apparent rarity of the disease in this country has led us to report the following case.

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From the Department of Pathology, Emory University School of Medicine.

Report of Case

A 7-month-old white boy weighed 6 lb. 10 oz. at birth, following normal gestation and delivery. Initial growth and development were normal, and at the age of 3 months he weighed 12 lb. 6 oz. He developed impetigo at the age of 4 months, which cleared completely after one injection of penicillin. One month later, he presented with a cough and low-grade fever. Examination revealed a temperature of 103.2 F and bilateral otitis media. He had failed to gain weight despite an adequate diet. He was treated with one injection of penicillin followed by tetracycline orally for six days. The otitis resolved, and the temperature returned to normal. During the following two months he continued to cough, occasionally producing a white sputum, and did not gain weight. At 6 months of age he was again examined, following a two-day period of anorexia and intermittent vomiting. Rectal temperature was 100.0 F, and both ear drums were again inflamed. Rales and rhonchi were heard for the first time over both lung fields, and slight cyanosis was observed after crying. After six days of oleandomycin and tetracycline therapy, the ear drums were clear but rales and rhonchi were still present. Therapy was continued for an additional week. During the following month he lost weight and developed a severe hacking cough. At the time of hospitalization he had respiratory distress and cyanosis of the nailbeds.

Family and Environmental History.—The patient had spent his entire life in Atlanta, in the two-room apartment of his parents, with the exception

of occasional visits to the farm of his maternal grandparents, 20 miles from Atlanta. The patient's mother was 22 years old, had always been in excellent health, and had had no previous pregnancies. The father was 26 years old and had a history of recurrent pulmonary infections following measles and pertussis during childhood. In 1951 he had had a resection of the lingula and lower lobe of the left lung. Review of the surgical specimen showed only bronchiectasis and pulmonary atelectasis. The apartment in which the child lived was said to have been clean, without infestation by roaches or other household pests. The child had not been exposed to dogs, cats, or other pets. The family had had no contact with anyone who had been in Europe. The maternal grandmother stated that she had had two boys who died in early infancy 25 to 30 years previously of a disease which seemed similar to that of the patient. However, she subsequently gave birth to seven additional healthy children. The farm home of the grandparents was clean, and it was stated that the patient had never been exposed to any of the farm animals.

Physical Examination.—Physical examination revealed a well-developed white boy who weighed 11.1 lb. He appeared acutely ill, with rapid hacking respirations and slightly cyanotic lips and nailbeds. The rectal temperature was 100.8 F; pulse rate, 160 per minute; respirations, 60 per minute. There was no palpable lymph node enlargement. The head, eyes, ears, nose, and throat appeared normal with the exception of considerable mucus in the external nares and a red, inflamed-appearing throat without exudate. The neck was supple and showed no evidence of venous distention. The thorax was symmetrical but moved vigorously during the rapid jerking respirations. A few scattered dry and medium moist rales were heard throughout both lung fields. The heart seemed somewhat enlarged, but the cardiac sounds were strong and no murmurs were heard. The abdomen was soft and nontender, and peristalsis was active. The liver was palpated 1 cm. below the right costal margin, and the spleen could not be palpated. The remaining general and neurological examination revealed no abnormalities.

Laboratory Data.—The blood hemoglobin was 15.2 gm. per 100 ml., and the WBC count was 16,950 per cubic millimeter, with a differential count of 73% segmental cells, 3% juvenile cells, 23% lymphocytes, and 4% monocytes. Urinalysis revealed no significant findings. Blood serum chemical determinations showed the following values: pH 7.52, CO_2 29 mEq. per liter, sodium 132 mEq. per liter, chloride 94 mEq. per liter, potassium 4.0 mEq. per liter, NPN 33 mg. per 100 cc. Stool trypsin activity was present in dilutions up to 1:100. First strength P. P. D. was negative after 48 hours. Chest roentgenograms revealed a small round heart which was difficult to evaluate because of the marked pulmonary changes. The cardiothoracic ratio was 6:13, and there was a suggestion that the apex was slightly elevated. There was diffuse increased density throughout both lung fields, somewhat more prominent on the left. The trachea and bronchi appeared patent, and there was no evidence of atelectasis or pleural changes (Fig. 1). The electrocardiogram revealed a sinus tachycardia (rate of 155 per minute) and some right ventricular hypertrophy.

Fig. 1.—Roentgenogram of chest showing diffuse increased density in both lung fields, more marked in left.

Hospital Course and Treatment.—The infant was placed in a Croupette and was given oxygen. The temperature remained normal during the entire hospital course. On the second hospital day he was digitalized with a total dose of 0.22 mg. of digitoxin during a 12-hour period. Antibiotic therapy was instituted on the second hospital day and consisted of aqueous penicillin, 500,000 units intramuscularly every six hours; tetracycline, 75 mg. orally every six hours, and chloramphenicol (Chloromycetin), 75 mg. orally every eight hours. The total dosages of the antibiotics administered were as follows: penicillin, 6,000,000 units; tetracycline, 780 mg., and chloramphenicol, 750 mg. On the fourth hospital day the respiratory rate had increased to 88 per minute and respirations were of a gasping character. Generalized deep cyanosis developed whenever the infant was removed from the Croupette or disturbed. This later became persistent, and on the fifth hospital day a tracheotomy was performed, without apparent improvement. Repeated chest roentgenograms and electrocardiograms showed no change.

The serum CO_2 content had fallen to 16 mEq. per liter, and the chlorides, to 90 mEq. per liter. Two intramuscular injections of 25 mg. of cortisone were administered. The infant vomited repeatedly, passed some loose stools, and died suddenly of respiratory arrest on the sixth hospital day.

Postmortem Examination.—A complete autopsy was performed 16 hours after death.

Gross Findings: The right lung weighed 120 gm. (normal, 39 gm.); the left, 122 gm. (normal, 42 gm.). The external and cut surfaces of the two organs were similar. The smooth and glistening pleura transmitted a light brown-yellow color which was less pronounced at the anterior edges. Crepitance was absent, and the consistency was rubbery. The cut surfaces were dry, with an accentuation of the alveolar markings. The color was mottled light brown with a slight yellow cast. The bronchi contained a small amount of yellow mucoid material but were not otherwise remarkable. The pulmonary vessels revealed no changes, and the hilar lymph nodes were normal.

The heart weighed 32 gm. (normal, 31 gm.) and was of normal size. There was no cor pulmonale. Marked cyanosis of the mucous membranes and nailbeds was present. The fingers and toes showed no clubbing. The thymus weighed less than 5 gm. but was of normal shape. The brain weighed 810 gm. (normal, 660 gm.). The middle ears were normal. A recent tracheotomy incision was present. The body was well developed and not emaciated.

Histologic Description: All tissues were fixed in Zenker's solution with 5% glacial acetic acid and in 10% formalin. In addition, lung tissue was fixed in Bouin's solution and in absolute alcohol. Smears were made from the cut surfaces of fresh lung tissue, some of which were air-dried while others were fixed in absolute alcohol. Sections of all tissues were stained with hematoxylin and phloxine. Giemsa and the Gomori methenamine silver stains were applied to sections of lung, spleen, liver, pancreas, adrenal, and kidney. Lung sections were also stained with the McManus-Schiff periodic acid, Gridley, Gram, Heidenhein iron hematoxylin, Mallory thionine, and phosphotungstic acid-hematoxylin methods. Formalin-fixed lung tissue was stained with Sudan III. The Giemsa and the Gomori methenamine silver methods were applied to the smears.

Numerous lung sections representing all lobes revealed similar pictures. The alveoli and respiratory bronchioles were distended with a dense spongy or honey-comb-like material which stained deeply eosinophilic with hematoxylin and phloxine, stained amphophilic with Giemsa stain, and was strongly PAS-positive, even after saliva digestion (Fig. 2). There was no fibrin. The alveolar contents were acellular except for some large mononuclear cells which had become detached from the septa, where they formed a prominent lining (Fig. 3). These cells, both free and attached, showed degenerative changes consisting of a bluish mucoid vacuolization of the cytoplasm as seen with the Giemsa stain and, less commonly, a foamy appearance which accounted for occasional patches of lightly sudanophilic material. The septa were diffusely thickened and showed some edema and infiltration by large mononuclear cells.

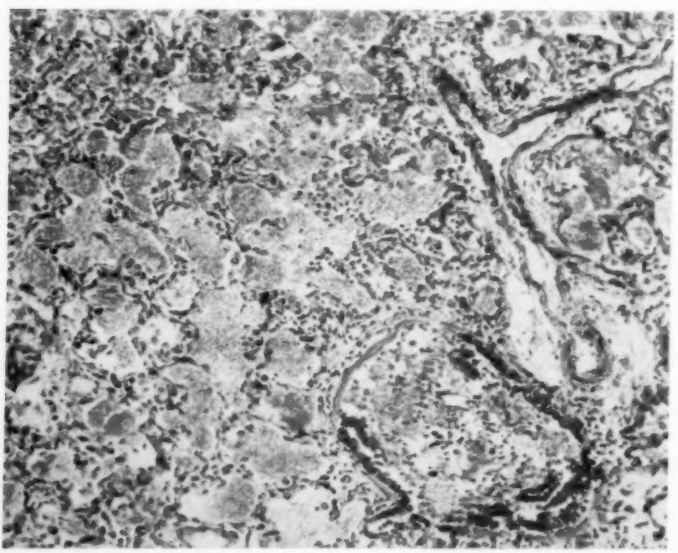

Fig. 2.—Lung. The alveoli contain a spongy exudate. Hematoxylin and phloxine; × 115.

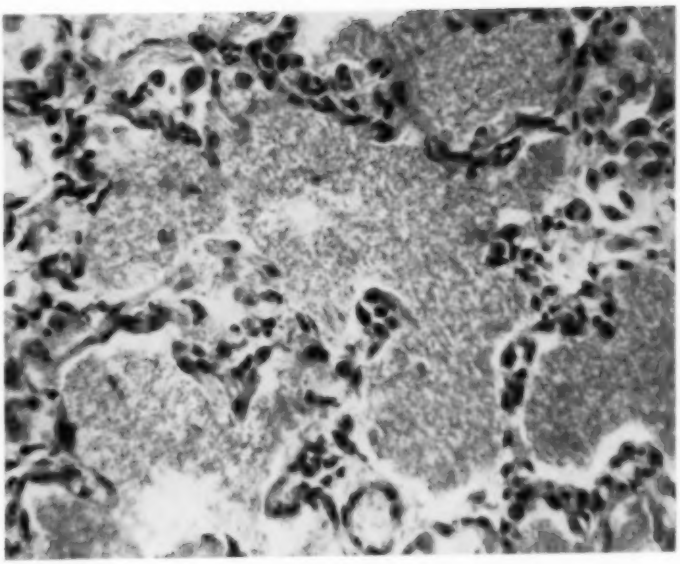

Fig. 3.—Lung. Acellular alveolar contents and thickening of septa. Giemsa; × 320.

No plasma cells were seen. A single minute focus of organization of the alveolar contents was noted, and in another small area a few multinucleated foreign-body-type giant cells were encountered. There was no necrosis. The larger bronchi contained occasional clumps of similar exudate intermingled at times with a few neutrophilic polymorphonuclear leukocytes. A slight acute inflammatory-cell infiltration was present in the wall and the surrounding connective tissue of a few bronchi. Except for congestion, the blood vessels were not remarkable. The pleura was normal.

The alveoli contained innumerable minute organisms singly, in the form of loose aggregates, or as small cysts. The organisms stained only faintly with hematoxylin but were best visualized with the Giemsa method. They were demonstrated less effectively with the Gram, iron hematoxylin, phosphotungstic acid-hematoxylin, and thionine stains. The cysts were best seen with Gomori's methenamine silver stain (Fig. 4), but the PAS

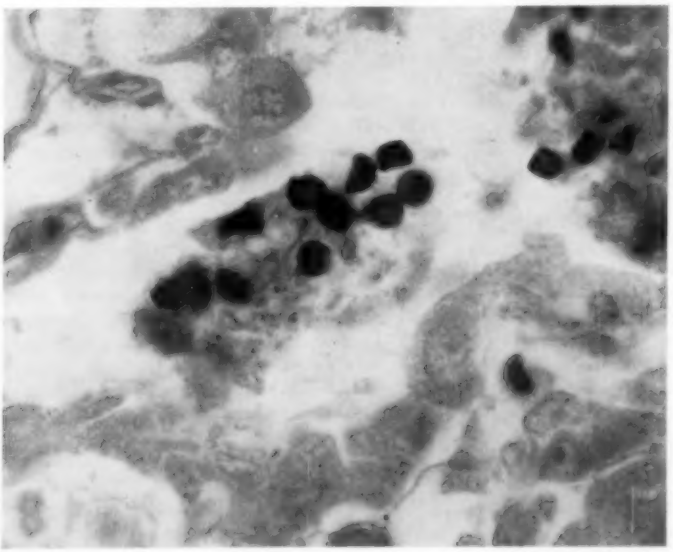

Fig. 4.—Lung. Cluster of Pneumocystis cysts (black) in alveolus with prominent lining cells. Gomori's methenamine silver-safranine; × 1500.

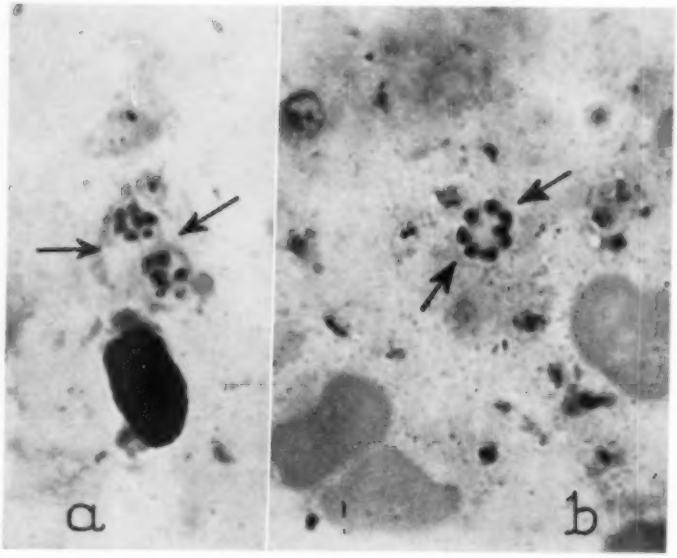

Fig. 5.—Lung smear, Giemsa. (*a*) Two Pneumocystis cysts (arrows). Alcohol fixation; × 1950. (*b*) Well-preserved Pneumocystis cyst with eight organisms (arrows) and faintly outlined capsule. Air dried; × 2000.

and Gridley methods also gave good results. The free, nonencysted, organisms also stained with these methods. The morphologic and tintorial characteristics of the organisms were best seen in Giemsa-stained smears. The free agents were round, oval, or elongated bodies, 2μ to 4μ in size, with a sky-blue cytoplasm and a dark violet nuclear mass surrounded by a variable amount of bluish-violet mucus-like material. The cysts varied from 6μ to 10μ in size and contained either 2, 4, 6, or 8 individual organisms (Fig. 5). No budding forms were seen. The cyst capsule appeared delicate.

The organisms were mostly seen in the interstices of the spongy alveolar contents. In only a few instances were they found intracellularly located in the cytoplasm of large mononuclear cells. These cells were either free among the alveolar contents or, even more rarely, attached to the septa. There was no convincing evidence that the organisms were present within the septa or other pulmonary tissues.

Pneumocystis organisms were searched for in sections of spleen, liver, pancreas, adrenal, and kidney, but none were identified. A similar unsuccessful search was made in all sections for cytomegalic inclusion disease.

Additional histologic findings consisted of cerebral edema, acute congestion of the viscera, lymphoid depletion of the spleen, marked involution of the thymus, lipid depletion of the adrenal cortex, and secondary hyperplasia of the bone marrow.

Final Anatomic Diagnosis: Pneumocystis carinii pneumonia, bilateral; tracheotomy, postoperative, recent; lymphoid depletion of spleen; involution, marked, of thymus; lipid depletion of adrenal cortex; secondary hyperplasia of bone marrow; cyanosis, marked, of nailbeds and mucous membranes; cerebral edema; acute congestion of viscera.

Bacteriologic Studies.—Thioglycolate broth cultures of heart blood and lung yielded no growth. Multiple tubes of Sabouraud dextrose agar inoculated with lung tissue and incubated at room temperature as well as at 30 C and 37 C yielded no fungus growth.

Additional attempts to isolate a fungus were carried out by Dr. Lucille K. George, Mycology Section, Communicable Disease Center, Department of Health, Education, and Welfare, Chamblee, Ga., who submitted the following report on a portion of lung tissue from our patient.

Direct examination of the material showed no fungal elements. Cultures were made on the following media: Sabouraud dextrose agar, Sabouraud dextrose agar with penicillin (20 units) and streptomycin (0.04 mg.); Sabouraud dextrose agar with penicillin (20 units), streptomycin (0.04 mg.), and cycloheximide (0.5 mg.), and brain-heart-infusion agar. All media were incubated at 20 C except the brain-heart-infusion agar tubes, which were incubated at 37 C. No fungi appeared in any of the culture tubes. Bacterial colonies on the brain-heart-infusion agar tubes were not identified.

Comment

The postmortem pulmonary findings in our patient and, in retrospect, the clinical

and roentgenologic data resemble in every respect the picture of Pneumocystis pneumonia as described by European workers.[9] Our study of a single patient does not contribute significantly to the understanding of the nature of the agent or the pathogenesis and morphology of the disease, but our observations, including the demonstration of the organisms in smears, do correspond closely to the extensive and careful studies of Vaněk, Jírovec, and associates.[10-12] Systemic dissemination has been reported in a few instances,[13] but we found no involvement of organs other than the lungs. Since some workers [14] have isolated a yeast, which they regard as the causative agent of this infection, our failure to grow a fungus is interesting.

Our patient differs in some respects from the majority of those observed in Europe. He was somewhat older than most reported cases, but the clinical findings suggest that the disease may have begun at the age of 6 months. The lungs showed neither fibrosis nor plasma-cell infiltration. The absence of plasma cells raised the question of agammaglobulinemia, which has been observed associated with Pneumocystis pneumonia in several patients.[5,15] No plasma was available for electrophorectic studies, but the presence of some plasma cells in other organs makes a disturbance of immune mechanisms seem unlikely. There was no evidence of any other debilitating disease. Some similar differences have also been noted in the three other cases of Pneumocystis pneumonia reported in this country.[2,3] In none of these was the infection associated with any other disorder. Two of the three patients were older than most of the European cases, being 14 and 21 months of age, respectively. Lastly, a sparse plasma-cell reaction in the lung was noted by Russell and Nelson [3] in one of their patients.

The American cases, including our own, all appeared to be sporadic instances of the disease. As yet, no epidemics have been reported in this country. It has been suggested that susceptible infants contract the disease either from adults with inapparent infection or from infected animals. Pneumocystis carinii is said to be present in many rodents, including those commonly used in the laboratory, and in many domestic animals as well as livestock. In our case, a careful but unrewarding search was made for contact with persons who had either been in Europe or gave a history of an unusual respiratory disorder. There was no known exposure to pets or other animals. The physicians in the patient's community are now aware of this disease but do not recollect a previous similar case, and no other infants with a syndrome suggestive of Pneumocystis pneumonia have been noted since.

The ineffectiveness of antibiotic therapy is emphasized by the course of our patient and corresponds with the experience of many others. Treatment with convalescent serum has been disappointing. Chemotherapy in general has been unsuccessful, but antiprotozoal and antifungal agents may deserve a more extensive trial. Cortisone and similar hormones would seem contraindicated, since they are known to lower host resistance.

The morphologic diagnosis of Pneumocystis pneumonia should no longer be difficult. The histologic findings in the lungs of most cases appear to be characteristic because of the peculiar spongy, or honeycomb-like, acellular alveolar exudate which contains the organisms. These can be demonstrated by a variety of stains in histologic preparations but are best visualized in imprint smears from the involved lung tissue. In the absence of an available laboratory test, the clinical diagnosis is more difficult, although in Europe it is made commonly. The disease is a persistent generally afebrile respiratory disorder of insidious onset progressing to severe dyspnea and tachypnea with cyanois. There is failure to gain weight and later actual weight loss. Cough, often nonproductive, may occur. Respiratory failure is the cause of death. The findings on physical examination are dis-

proportionally slight and consist only of fine crepitant rales and rhonchi and areas of slightly decreased resonance and bronchial breathing. Roentgenologic changes in the lung seem to appear early in the disease and consist of spreading patches of soft infiltration alternating with areas of emphysema and atelectasis. The laboratory findings are noncontributory, but some compensatory polycythemia may occur in the later stages. Demonstration of the organisms is at present the best means to ascertain the diagnosis. Giemsa-stained smears of material obtained by lung puncture are said to have been used with some success. In rare instances only have the organisms been found in smears of saliva and of mucus from the larynx and bronchi. They have also been seen in thick drop preparations of peripheral blood.[9] A skin test has been developed, but the results are uncertain.[11] Several attempts to devise a complement-fixation test are reported, and some have given good results, but we are not aware that the test is presently available in this country.[16]

It will be interesting to see if Pneumocystis pneumonia is truly a rare disease in this country. A review of the files in the pathology laboratories of children's hospitals should show if the infection has been overlooked in the past. Awareness of the disease by pediatricians may lead to the clinical recognition of additional cases, particularly those which are not fatal.

Summary

An isolated case of Pneumocystis carinii pneumonia is described in a 7-months-old white native American boy. The organisms were identified in histologic sections and in imprint smears of the lung.

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Electroencephalography in Subdural Hematoma and Effusion in Infants

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The difficulties in the clinical diagnosis of subdural hematoma and effusion in infants are well known. The symptoms and signs are in many cases nonspecific, especially in the early stages of the disease.[1] A history of trauma, which has been considered to be one of the main causes of this disease, can be elicited only in a minority of the cases. Other conditions, such as malnutrition, diarrhea, meningitis, and bleeding tendencies, are today known etiological factors for the production of fluid in the subdural space. Such a collection of fluid is frequently accompanied by changes in the brain (swelling, atrophy) and by the formation of membranes. These changes may form the basis for later convulsive disorders and disturbances in somatic and mental development. Early diagnosis and early surgical treatment are, therefore, of paramount important, since a proper surgical procedure may provide a complete cure and prevent later complications.

A definitive diagnosis can be made by a subdural puncture through the open fontanel which reveals xanthochromic or bloody fluid. This procedure, however, is not without risk, because of the possibility of hemorrhage and the subsequent development of a subdural hematoma. On the other hand, if this diagnostic test is delayed for some time not only may the fontanels close, necessitating bur holes for the establishment of the presence of fluid in the subdural space, but irreversible damage to the brain may result.

Electroencephalography has for a long time been known to yield abnormal records in subdural hematoma in adults.[2-7] In infants, however, the use of the EEG in the diagnosis of subdural hematoma has rarely been mentioned. Several authorities have considered the EEG to be of little help in the diagnosis of this condition. Elvidge and Jackson[8] point out that EEG is not necessary in the diagnosis of subdural hematoma in infants, since the patients are too young for its satisfactory employment. Ingraham and Matson,[9] in their comprehensive publication on this subject, make no mention of electroencephalography in the establishment of the diagnosis of this condition. Ford[10] also fails to mention the use of EEG in the diagnosis of chronic subdural hematoma. There are only a few reports dealing exclusively with EEG findings in subdural hematoma in infancy.[11-13] Since we had been impressed by the presence of EEG disturbances in infants with subdural hematoma and effusion, it was decided to review our material with the particular aim of determining (1) whether the EEG examination may be of help in the establishment of this diagnosis and (2) what changes were present in the records of such cases.

Material and Methods

This series includes 14 infants with a collection of fluid in the subdural space and membrane formation. In all infants the diagnosis was established by subdural puncture and was finally confirmed by operation. The collection of subdural fluid was bilateral in 11 cases and unilateral in 3. The ages of 13 infants were distributed between 3 and 9

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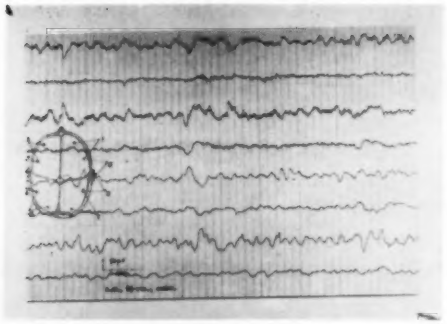

Fig. 1.—Generalized flattening with suppression of α-activity on the pathological side.

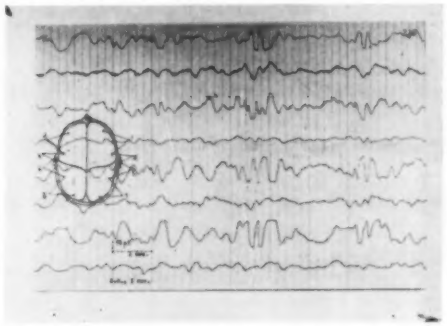

Fig. 2.—Flattening and absence of burst activity on the pathological side.

months; the remaining patient was 19 months old at the time when the electroencephalogram was recorded. The clinical features, the operative findings, and the postoperative course of these cases have been published in a previous paper[14] and will not be repeated here. Three infants who were admitted to this hospital after the conclusion of the previous paper, have been added to this series.

Records were taken on a Grass eight-channel machine; 18 electrodes were placed routinely and additional ones whenever required. In most cases there was no need for sedation and records could be obtained while the children were awake and asleep. This admittedly required a great deal of patience on the part of the technicians. Whenever sedation had to be employed secobarbital (Seconal) sodium, orally or rectally, was used. The evaluation was done according to the rules laid down by Gibbs,[15] Strauss,[16] and Hill and Parr.[17] In seven of our cases follow-up studies were possible and repeated tracings were done three months to two years postoperatively.

Results

The preoperative EEG records of 13 of our 14 patients were definitely pathological. Their basic activity was constituted by slow waves of usually excessively high voltage. In 11 of these records a reduction of voltage ("flattening," "suppression") (Figs. 1 and 2), occasionally down to almost complete "electrical silence" (Fig. 3), was present in the curves obtained from certain regions of the brain. This flattening in most of the cases was observed in the derivations from the temporoparietal areas; it sometimes extended, however, over the whole of one hemisphere. In one of these 11 cases, showing flattening, where sleep had to be artificially induced by the administration of secobarbital sodium, there was only little "barbiturate fast activity" present in the flattened curves obtained from the pathological brain region. This artificially induced fast activity was well recorded from the other brain areas.

In the two cases where no flattening was present, the disturbance of electrical brain activity was demonstrated by slow waves, which were diffusely distributed throughout the record. In our last case the electroencephalogram was classified as within normal limits. This case, a 6-month-old infant, had a unilateral subdural effusion after Hemophilus influenzae meningitis. The EEG was taken 10 days after the beginning of the disease, and in spite of a considerable amount of fluid in the left subdural space no abnormalities were discernible in the EEG curves.

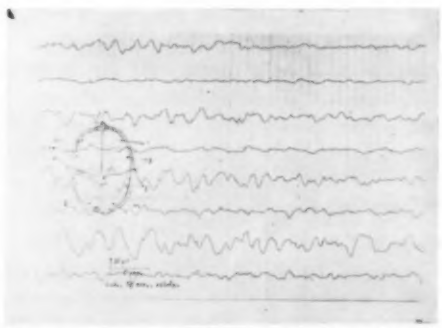

Fig. 3.—Sleep record showing "electrical silence" recorded from the anterior part of the left hemisphere.

Comment

Since Walter's report, in 1940,[18] of a "silent area" over an extradural hematoma, there has been a steadily increasing number of publications dealing with this subject.[2-7] These reports concerned themselves mainly with the EEG changes in adults and included only very few cases of children, hardly any of infants. The EEG changes which have been reported in adults include (1) "flattening" (reduction of voltage) over the area of the lesion, (2) suppression of α-activity on the side of the lesion, (3) generalized diffuse slowing of the brain activity, and (4) focal slowing of brain activity. Almost all observers reported on the occurrence of normal records in their material, even in patients with large amounts of subdural fluid.

In contradistinction to this considerable number of articles dealing with adults, we could find only three publications on the EEG findings in children and infants.

Marinacci et al.[11] reported on six infants and on one child aged 4 years. In three a diffuse abnormality, consisting of an absence or suppression of cerebral activity, was noted. In the remaining four patients asymmetric records with local hemispheric changes were found.

Grützner et al.[12] examined 29 children with subdural effusion. In 73.9% of their patients they correctly determined the side of the effusion in unilateral cases or the side of the larger effusion in bilateral cases. They considered slowing of brain activity to be of much greater diagnostic importance than reduction of amplitude. It was their conclusion that EEG may have the same positive value in the diagnosis of this condition in infants as in adults. The prognostic value of EEG could not, however, be clearly determined.

Ferrier et al.[13] reported on their findings in three children with traumatic subdural hematoma and found a unilateral flattening of the basic rhythm in each case.

Mention should be made of Rodin and co-workers,[7] whose reported group included five infants and three children. These investigators found EEG not very helpful in localizing unilateral hematomas but more effective in indicating the presence of an organic lesion in bilateral cases.

In the review of these studies, as well as our own findings, EEG suggests itself as an important diagnostic tool. The described changes have been either slowing of activity (slow waves, mostly of high voltage) or asymmetrical lowering of amplitude. Slowing of the frequency of electrical brain rhythms denotes a disturbance of brain function. A lowering of amplitude, apart from "arousal phenomena," may be due either to the presence of a dielectric (fluid, foreign material, thickened membranes, etc.) between the cortex and the recording electrodes or to a reduction in the activity of the brain. Another change, found in only one of our cases, but worth mentioning, was the unilateral, regional absence of induced barbiturate fast activity in the derivations from the pathological area. Such a regional abolition of induced fast activity has been described as an aid in the EEG location of cerebral lesions.[19] These changes in the EEG, described in the literature and found in our cases, are not pathognomonic for subdural hematoma or effusion, since other pathological conditions may cause similar changes (e. g., local encephalopathy, cortical atrophy, occlusion of a major cerebral blood vessel, porencephalic cyst).

In the cases with bilateral effusions we were not able to find any correlation between the degree of the electrical changes on the one hand and the amount of fluid, the side of the larger effusion, or the side of the thicker membrane on the other hand. We therefore are not able to substantiate the report of other workers stressing the high lateralizing and localizing value of the EEG.[12] This, however, does not detract from the practical value of EEG in this condition, since the suspicion of the presence of an effusion definitely necessitates the performance of taps or bur holes on both sides.

It should be stressed that occasionally normal records have been obtained from patients with subdural collection of fluid. This was the case in our last patient, i. e., in 1 of a group of 14 patients. On the other hand, the high incidence of abnormal EEG curves and particularly changes of a specific type, i. e., flattening, point to the value of this harmless and relatively simple examination in infants clinically suspected of suffering from subdural hematoma or effusion. The number of cases surveyed in this study is too small to allow any definite conclusion. However, the results basically correspond to those of other investigators on this subject, and the impression may be justified that since the diagnosis of subdural hematoma and effusion has to be made on nonspecific signs and symptoms, an abnormal EEG may supply additional weight in favor of the immediate performance of a subdural puncture. A normal electroencephalogram, on the other hand, may justify a more expectant approach and, in the absence of other conclusive clinical signs, permit a postponement of the performance of a subdural puncture.

Postoperative EEG curves were recorded in seven of our cases. Unfortunately, this follow-up study could not be carried out systematically and therefore our material does not lend itself to a critical appraisal of the prognostic value of the EEG in subdural hematoma and effusion in infants. It should, however, be mentioned that in infants with a normal postoperative development the EEG's became either completely normal or showed only a slight residual regional flattening on a background that had become normal. In one case where the membrane could be removed on one side only, the EEG record, taken 20 months postoperatively, revealed a disturbance over the side where the membrane had been left in place. This child, in fact, was retarded both mentally and physically.

Summary

EEG records of 14 surgically verified cases of subdural hematoma and effusions in infants are reviewed. Abnormal curves were obtained in 13 cases. These abnormalities consisted in a reduction of voltage ("flattening") and slowing of the electrical brain activity in 11 cases, while there was only a general diffuse slowing in 2 cases. In one case the EEG was rated as within normal limits.

The high incidence of abnormal records in our series points to the value of the EEG in the diagnosis of this condition. Although the EEG changes are not specific and pathognomonic for this clinical entity, this harmless and relatively simple examination may help in the diagnosis of subdural hematoma and effusion in infants. An abnormal EEG record necessitates a performance of a subdural puncture or bur holes; a normal EEG justifies a more conservative approach.

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Epidemic of Diarrhea of the Newborn—Nonassociation of Cytopathogenic Agents

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Investigations of the past decade have made it clear that certain serotypes of Escherichia coli are capable of causing diarrheal disease in infants. Such enteropathogenic E. coli appear to be responsible for many of the recently studied institutional epidemics [1-6] and account for part of the sporadic diarrheas occurring in infancy.[7-9] On the other hand, as a result of the development of newer tissue culture techniques, recently discovered viruses have been shown to be associated with diarrheal disease. Thus Ramos-Alvarez [10] found a significant relationship between the incidence of certain enteric cytopathogenic human orphan (ECHO) viruses and "summer diarrhea" in infants and children, and Eichenwald et al.[11] have recently reported a nursery outbreak in which cytopathogenic agents were recovered from 10 of 12 infants who had diarrhea.

In view of such findings, it has become necessary to examine the possible role of viral agents in all forms of diarrhea, including those in which the etiologic significance of enteropathogenic E. coli has been demonstrated. It is the purpose of this paper to report the findings with respect to cytopathogenic viruses in an epidemic previously described by us [3,12] in which E. coli O127:B_8 was the etiologic agent. This study was undertaken in order to determine the incidence of cytopathogenic viruses under the conditions of such an epidemic, and in case such agents were demonstrated to learn what role they might play in the causation of disease.

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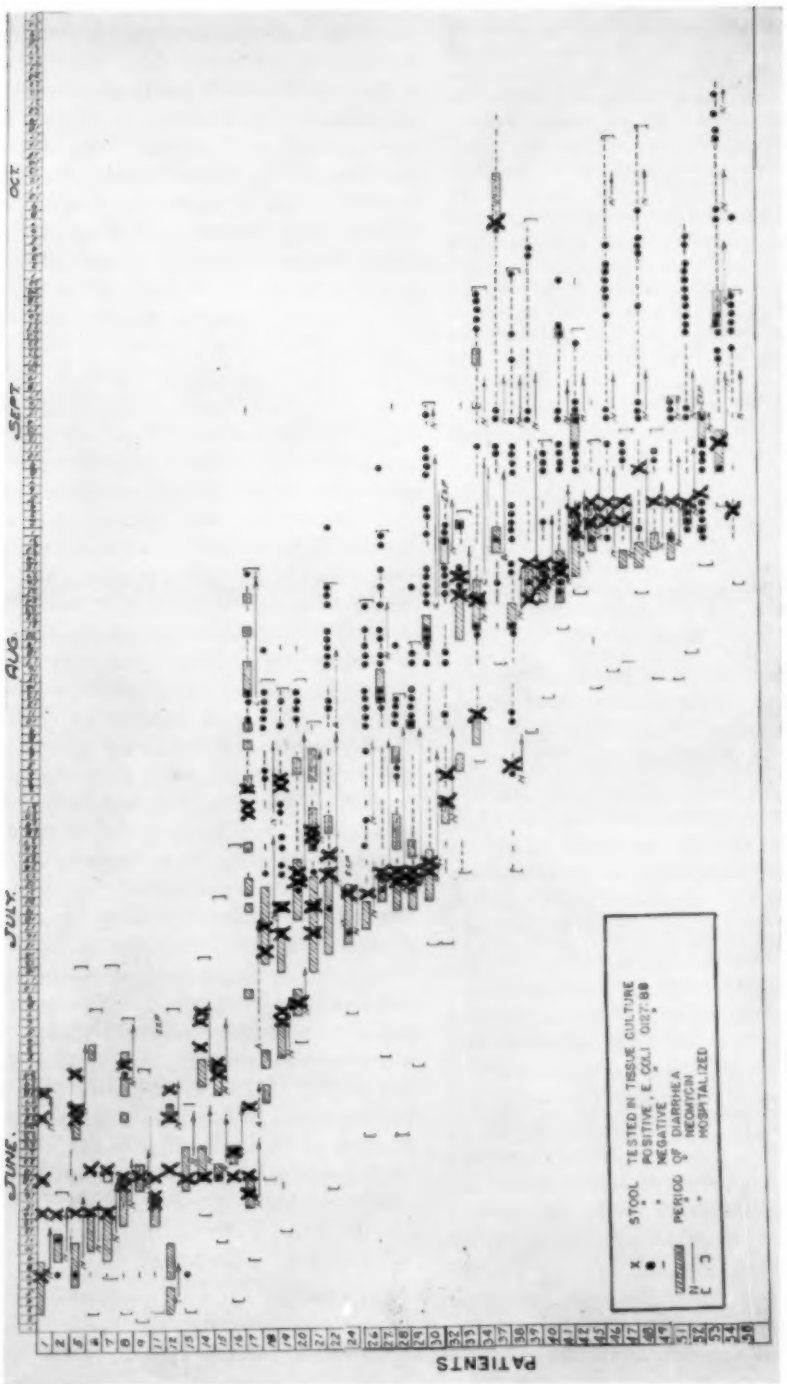
Subjects Studied

An outbreak of diarrhea in the premature nursery of this hospital was described in detail in a previous communication.[8] The epidemic, which involved a total of 60 cases over a period of four months, was characterized by a cyclic series of flare-ups. E. coli O127:B_8 was isolated in virtually pure culture from the stools during the acute stage of the disease, and both organisms and symptoms disappeared when the sick infants were treated with neomycin. However, with the cessation of the antibiotic, each new cycle began with the reappearance of the enteropathogens in the stools, resulting invariably in asymptomatic carriers, clinical relapses, and new infections. The Figure illustrates the clinical course and bacteriologic findings in each of 45 of the infants from whom stool specimens were obtained which were preserved for future virus studies.

Virologic Methods

Preparation of Stools.—Solid stools and portions of diaper containing liquid stools were tightly sealed in jars and stored at —20 C. These specimens were later thawed and suspended in approximately 20% dilution in basal medium (Eagle [13]), to which antibiotics were added. These suspensions were then centrifuged at 2500 g for one hour under refrigeration, and the supernates were again similarly centrifuged. If the final supernates exhibited an acid pH, they were adjusted to pH 7.2 with bicarbonate.

Tissue Culture Procedures.—Monkey kidney cultures, HeLa cultures, and Detroit-6 cultures [14] either were obtained from Microbiological Associates, Inc., Bethesda, Md., or were prepared in our own laboratory. Two cultures of each cell type, i. e., a total of six cultures, were selected for inoculation with each stool supernate. Before



Forty-five cases from an epidemic of diarrhea in a premature nursery, showing periods of diarrhea, incidence of E. coli O127:B8, antibiotic therapy, and distribution of stools tested for cytopathogenic agents.

inoculation each culture was washed with basal medium. One-tenth milliliter of stool supernate was placed directly on the cellular monolayer and was allowed to adsorb for 20 minutes. One milliliter of a medium consisting of basal medium 95%, calf serum 5%, and the usual antibiotics was then added to each tube. All calf sera used in these experiments were shown to be devoid of inhibitors for 16 ECHO virus types and for polioviruses. Uninoculated control cultures were included for comparison with each inoculated series.

The cultures were incubated in a stationary position at 36 C for as long as the integrity of each cell type permitted, usually 2 to 3 weeks for monkey kidney and 7 to 10 days for HeLa or Detroit-6 cells. Occasionally, the development of an acid pH required changes of the medium. Each culture was observed daily for evidence of cellular degeneration. If at any time the cells exhibited (*a*) a slight degree of degeneration that did not progress, (*b*) progressive cellular degeneration, or (*c*) marked degeneration in 24 to 48 hours, the culture fluids were passed into a second series of each culture type and similar observations were made.

Results

The Figure illustrates the distribution of 95 stool specimens obtained from 45 infants who had diarrhea. In addition, eight stool specimens were collected from five infants who were not listed in the Figure but who were admitted to the nursery at the end of the epidemic and who were not ill and did not excrete enteropathogenic E. coli at any time. From nine infants (Patients 1, 5, 8, 14, 17, 18, 19, 20, 21) three to six specimens were obtained during periods of diarrhea and convalescence, including periods of bacteriologic and clinical relapses. From 11 additional infants one or more stools were obtained during the acute illness and one or more at some time during convalescence (Patients 7, 11, 12, 15, 22, 32, 33, 34, 39, 42, 45). From the remainder, specimens were obtained either while the infant had acute diarrheal disease or during convalescence. From one infant a specimen was obtained several weeks before diarrhea appeared, and three specimens were obtained from two infants who did not contract diarrhea but who nevertheless excreted enteropathogenic E. coli.

Of a total of 103 stool specimens, 42 produced some nonspecific degeneration of cells in HeLa or Detroit-6 cultures during the initial passage. Only rarely was more than one culture tube involved. None of these specimens affected monkey kidney cells. On the premise that these effects might nevertheless be due to viruses, the fluids from each of these cultures were transferred to fresh cultures of each of the three cell types (second passage). In no instance could cytopathogenic agents be recovered in second passage.

The cell degeneration observed during first passage was therefore considered to be due either to toxicity of stool material for the more sensitive HeLa and Detroit-6 cells or to spontaneous degeneration occurring in the cultures. In those cultures that were thought to be affected by "toxic" stool extracts, usually all the cells in a culture degenerated within 24 hours, and such effects could not be duplicated in second passage. It is unlikely that if enough virus was present to produce such rapid and marked degeneration it would not be passable on transfer. In some instances minimal cellular degeneration was seen in cultures 2 to 10 days after inoculation, but when this occurred, similar effects were often noted in control cultures. Again, fluids from these cultures did not produce cytopathogenic effects in any of the three tissue culture systems on second passage.

In only one instance was a possible cytopathogenic agent observed. A specimen obtained on June 18 from Patient 12, at a time when he was asymptomatic but excreting E. coli O127:B_8, produced progressive cellular degeneration in all three tissue culture systems, and fluids from these passed separately into fresh cultures again affected the cells in the same manner.

Comment

Of a total of 103 stool specimens obtained from 50 infants during the epidemic, only 1 yielded a possible cytopathogenic agent. It appears therefore that cytopathogenic

viruses are not implicated in the etiology of this particular outbreak, while, on the other hand, the bacteriologic studies previously reported clearly demonstrated the role of an enteropathogenic strain of E. coli, namely, E. coli O127:B_8.

The absence of detectable viruses with or without pathogenic activity in this group of patients is not surprising in view of the fact that the patients were newborn infants who did not have the usual exposure to viruses that might be prevalent in the community. All were premature infants who had entered the nursery within a few hours after birth from obstetrical units of other hospitals, and the majority were under 4 weeks of age when they contracted diarrhea.

Information on the incidence of viruses of the intestinal tract of the newborn infant is as yet lacking. Gordon and Whitney [15] reported the absence of cytopathogenic agents (as well as of known serotypes of enteropathogenic E. coli) in an outbreak of diarrhea in a newborn nursery. In older infants and children, Ramos-Alvarez and Sabin [16] have shown that the highest percentage of ECHO virus carriers occurs between the ages of 1 to 4 years and that the carrier rate then diminishes with increasing age.

It has been pointed out that outbreaks of E. coli diarrhea are not difficult to distinguish from other types of diarrheal disease on clinical and epidemiological grounds as well as by cultural criteria.[17] In the outbreak described herein the clinical and epidemiological features conformed to those now known to be associated with diarrhea due to enteropathogenic E. coli. The absence of cytopathogenic viruses not only completes the evidence that E. coli O127:B_8 was the sole causative agent but permits a further differentiation of the diarrheas of infancy and their causes.

Summary

In an epidemic of infantile diarrhea in a premature nursery in which bacteriologic studies had demonstrated the etiologic role of Escherichia coli O127:B_8, a systematic search for cytopathogenic viruses revealed no evidence of their presence or etiologic significance.

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Skin pH Pattern in the Newborn Infant

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A markedly acid surface reaction is a characteristic attribute of the healthy human skin. The physiologic occurrence of strictly localized zones where acidity is diminished has been the subject of previous reports [1,2]; they deal primarily with differences among the skin pH patterns of children, adolescents, and adults.

Little is known about the skin pH of infants during the first month after birth. The only pertinent investigation known to us is that of Taddei.[3] His findings uniformly demonstrate that the skin pH is maintained in the neighborhood of 6.5 from birth through the 20th day. The presence of such uniform and relatively elevated values would tend to indicate that the mechanism responsible for the physiologic acidification of the skin surface has not yet developed in these young infants.

Our own studies do not confirm Taddei's findings. It is the purpose of this communication to report the results of skin pH determinations obtained from a series of infants from birth through the first month and to discuss the physiologic implications.

Subjects Tested and Methods of Examination

The report is based on 945 individual pH determinations carried out in 222 subjects ranging in age from 1 hour to 30 days. Serial determinations were done on 27 infants; all other subjects were tested at one age only. The whole series includes 109 boys and 113 girls; of these, 64 were Caucasians; 60, Negroes, and 98, Puerto Ricans. They were selected from hospital nurseries, wards, and a few from private practice. They were healthy full-term babies of not less than 5 lb. (2470 gm.), afebrile and without noticeable disease. Some of the older infants were convalescing from illness or surgery. The presence of skin eruptions excluded selection for testing.

Skin pH determinations were carried out according to the colorimetric method of Bernstein and Herrmann,[4] with slight modifications as described and evaluated in earlier reports.[1,2] A solution * prepared according to the originally recommended formula served as indicator throughout. In addition to the requirements applying to colorimetric skin testing in general, some special precautions were felt to be in order prior to testing newborns. The use of soaps, detergents, or other chemicals was strictly avoided. Only plain water was used for routine cleansing of the skin after birth. Application of baby toiletries prior to and during the test period was prohibited.

As in earlier investigations, the results were checked potentiometrically, at times, by means of the Beckmann pH meter, in conjunction with the special glass electrode devised for the examination of minute traces of aqueous material on small surface areas.[5]

With a few exceptions, the skin pH was tested in each infant and at each session at three sites: (1) on the shoulder where the deltoid covers the acromion; (2) on the armpit, in an area roughly corresponding to the axillary vault, and (3) on the abdomen at a site at least 2 in. lateral to and either just proximal to or just distal to the navel. Separate testing of axillary vault and fossa as practiced in our studies on children and adolescents is not feasible in young infants. Their armpits show an anatomic configuration which prohibits a clear distinction between these two areas. Moreover, in a large series of newborns in whom such differentiation was attempted no significant difference between vault and fossa pH could be demonstrated. In a small number of subjects an additional skin region was tested, i. e., the center of the extensor surface of the thigh.

Results

The data collected on the main series of 209 infants consist of a total of 729 in-

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* Universal Wide Range Indicator (Harleco), sold by Standard Scientific Supply Corp., New York.

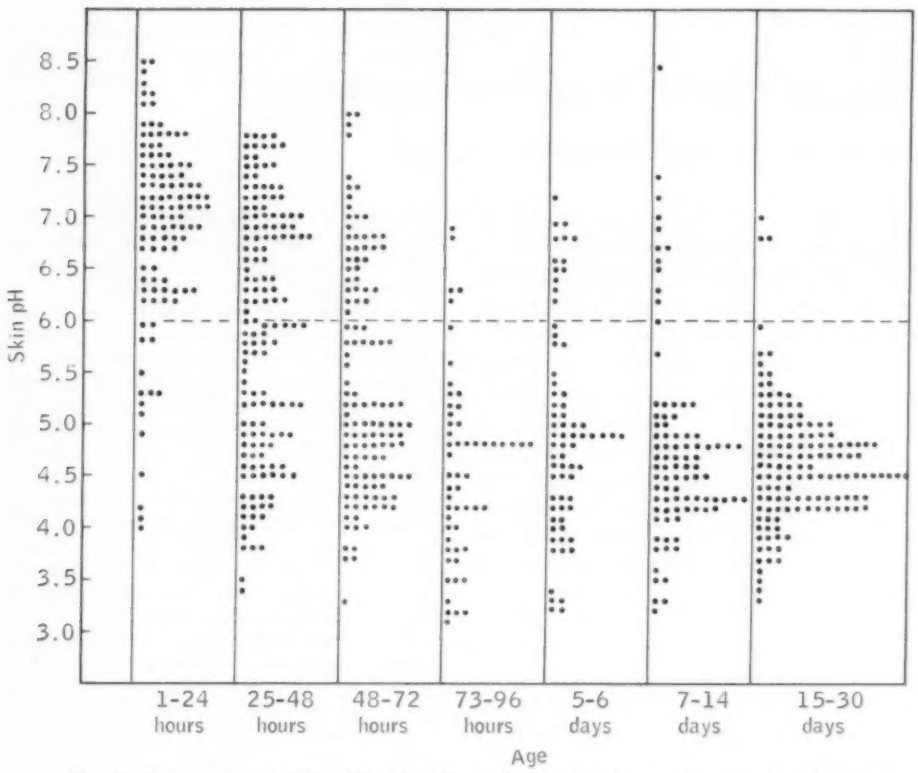

Fig. 1.—Scattergram showing 729 skin pH readings (shoulder, axilla, abdomen) in 209 infants arranged by age groups.

dividual readings taken from the axilla, shoulder, and abdomen. The scattergram (Fig. 1) gives an over-all picture of the distribution of these readings by age, without reference to specific skin areas. During the first 24 hours of life there is a marked preponderance of pH values above 6.0, with many readings exceeding 7.0. In the group of newborns 25 to 48 hours of age there is already an obvious shift towards more acid values and a relative decrease in the incidence of higher pH readings. During the third and fourth days of life this trend towards an increasing proportion of more acid values becomes still more obvious. This proportion remains relatively constant during the following nine days. Finally, between the third and fourth weeks of life, the characteristic "acid" pattern of childhood and adulthood becomes established.

To express these findings in quantitative terms it was necessary to divide the test subjects into age groups of comparable numbers. Guided by what the scattergram indicates, we felt justified in setting up three age groups, with approximately 240 observations listed in each: Group I, including newborns 1 to 48 hours old; Group II, newborns 3 to 6 days old; Group III, newborns and infants 7 to 30 days old.

Table 1 shows the distribution of the 729 readings as related to these three age groups and the three test areas. It can be seen that high pH values prevail during the first 48 hours, whereas with advancing age the skin acidity is rising. In Group III only an occasional pH value above 6.0 is found. Although this trend is clearly discernible on all three sites tested, some differences will be noticed. Readings on the abdominal wall are

TABLE 1.—*Distribution of pH Readings in Infants by Age and Skin Region*

Age Group	Skin Area Tested	Individual Tests, No.	Infants in Each pH Range, No.					
			3-3.9	4-4.9	5-5.9	6-6.9	7-7.9	8.0
I (1-48 hr.)	Shoulder	87	3	23	17	21	21	2
	Axilla	86	3	16	9	23	33	4
	Abdomen	82	0	3	9	29	39	2
II (3-6 days)	Shoulder	85	21	40	13	10	1	0
	Axilla	83	7	36	20	16	2	0
	Abdomen	82	2	31	18	22	7	2
III (7-30 days)	Shoulder	76	16	54	3	2	1	0
	Axilla	75	8	41	22	3	1	0
	Abdomen	73	2	47	15	6	2	1

TABLE 2.—*Mean Values of Skin pH by Age Groups (249 Test Subjects)*

Site	Skin pH in Each Age Group		
	I	II	III
Shoulder			
Mean	5.8	4.7	4.4
S. D.	1.27	0.96	0.67
Axilla			
Mean	6.3	5.0	4.7
S. D.	1.2	1.03	0.7
Abdomen			
Mean	6.8	5.6	4.9
S. D.	0.83	1.06	0.79

still of a relatively high pH range when the values obtained in the other areas, particularly on the shoulder, have decreased considerably. This applies to all age groups.

Table 2 gives the mean pH values as calculated for each age group and test area. These figures are representative of the normal sequence of changes in skin pH during the newborn period. The same trend is clearly discernible in measurements obtained from four newborns who were tested daily up to one week of age (Fig. 2).

Table 3 shows the results of pH determinations obtained from corresponding skin areas, left and right, of the same infants after removal of the vernix from half of the body surface within the first hour after delivery. Water only was used for cleansing off the vernix. Significant differences between pH readings obtained from corresponding areas are not noticeable. However, the tendency for pH values to decline with advancing age is evident on both "cleaned" and "uncleaned" sides of the surface.

Table 4 records the pH readings obtained from six infants who were cleaned on one side with water only and on the other with dehydrated alcohol (absolute ethyl alcohol). Again, the differences in pH between left and right, water-cleaned and alcohol-cleaned, areas are insignificant, but the described tendency of the pH values to decline with advancing age is obvious.

The results of 24 electrometric control examinations showed satisfactory agreement with our colorimetric readings. Confirming earlier experience,[1] the pH values ob-

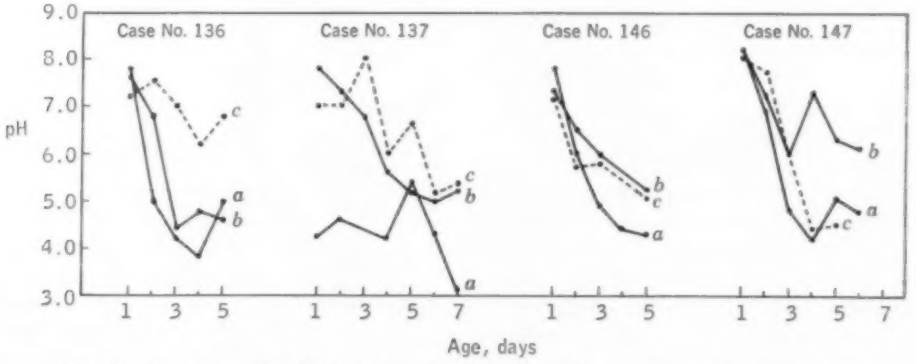

Fig. 2.—Changes in skin pH during the first week after birth as observed in four infants. (*a*) Shoulder; (*b*) axilla; (*c*) abdomen.

TABLE 3.—*Surface pH on Correspondent Skin Areas—Water-Cleaned on One Side, Not Cleaned on the Other*

	Cleaned				Not Cleaned			
	Thigh pH	Shoulder pH	Axilla pH	Abdomen pH	Thigh pH	Shoulder pH	Axilla pH	Abdomen pH
Infant 1								
1st day	5.2	5.3	5.2	5.8	7.0	6.2	6.8	7.5
2d day	4.9	5.1	4.8	5.4	4.8	7.0	4.9	6.3
3d day	5.1	4.7	4.3	5.4	7.9	4.9	4.1	8.1
Infant 2								
1st day	5.8	7.0	6.8	6.6	6.8	6.8	6.2	7.0
2d day	5.2	6.4	6.0	6.8	4.2	6.5	5.0	6.8
3d day	8.0	7.2	4.3	7.9	4.7	7.2	5.1	7.6
Infant 3								
1st day	7.2	6.8	5.8	7.4	7.3	4.5	5.4	7.8
3d day	5.0	4.2	5.0	5.1	5.3	4.4	4.8	5.2
Infant 4								
1st day	6.8	4.9	5.0	7.5	6.0	5.9	5.5	8.0
3d day	4.4	4.0	4.2	6.4	3.9	4.2	4.9	6.8

TABLE 4.—*Surface pH on Correspondent Skin Areas—Alcohol-Cleaned on One Side, Water-Cleaned or Not Cleaned on the Other*

		Right Side				Left Side		
No.	Age, Hr.	Treatment of Test Area	Skin pH			Treatment of Test Area	Skin pH	
			Shoulder	Axilla	Abdomen		Shoulder	Axilla	Abdomen
1	1	Water-cleaning				Water-cleaning			
	9					Alcohol-cleaning			
	10		4.9	4.8	6.0		4.5	5.0	4.8
	34		5.0	4.9	4.3		5.0	5.3	4.8
2	1	Water-cleaning				Alcohol-cleaning			
	2		6.9	7.2	7.8		6.2	6.5	6.1
	26		5.3	6.8	7.2		6.2	4.3	7.3
	76		4.2	3.9	6.3		4.2	4.5	6.8
3	1	No cleaning				No cleaning			
	1.5					Alcohol-cleaning	7.4	7.1	7.5
	2						7.5	7.3	6.9
	25		6.7	6.8	6.6		6.4	6.3	6.2
	74		4.0	3.4	4.9		3.8	3.5	4.6
4	1	No cleaning				No cleaning			
	2		6.9	7.4	7.2		7.0	7.1	7.4
	2.5					Alcohol-cleaning			
	3.5		7.1	6.4	7.3		5.0	6.8	7.3
	27		6.0	6.2	7.0		4.8	6.8	7.2
	75		3.8	5.0	5.8		4.8	4.8	6.0
5	1	Water-cleaning				Water-cleaning			
	5		6.7	7.5	7.0		6.9	7.3	7.2
	7					Alcohol-cleaning			
	8		6.8	7.0	7.0		7.3	6.9	6.8
	33		3.8	4.0	6.3		4.0	4.8	6.5
	55		3.6	3.8	5.8		4.3	4.4	6.3
6	1	Water-cleaning				Water-cleaning			
	2		7.0	6.9	7.2		7.1	7.4	7.4
	2.5					Alcohol-cleaning			
	3.5		7.4	6.7	7.0		6.3	6.8	6.7
	26		4.8	6.3	7.0		6.0	6.8	7.3
	48		5.0	6.1	6.9		4.8	4.3	5.6

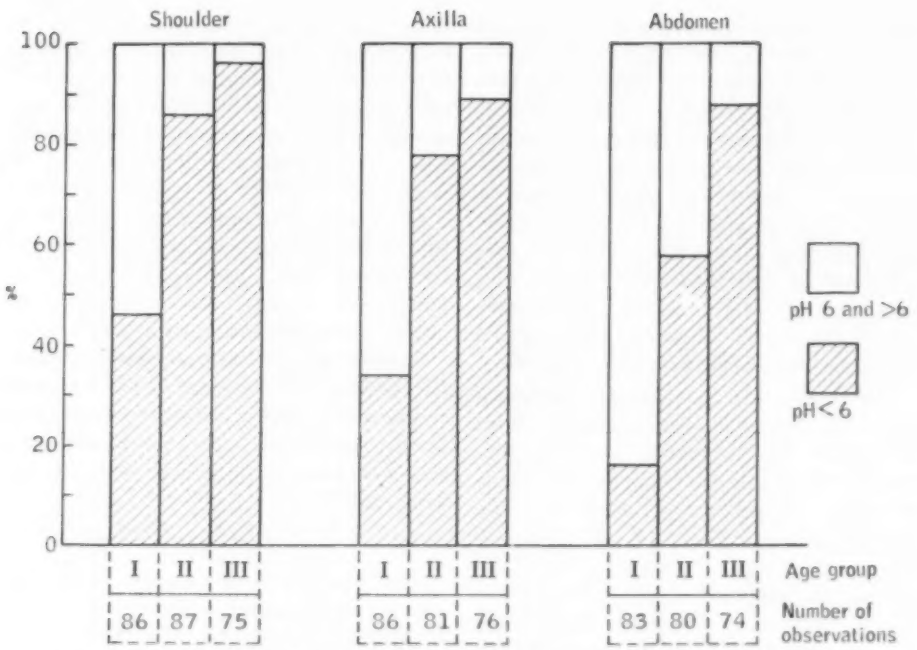

Fig. 3.—Percentage distribution of pH readings on three test areas by age groups. Group I, age 1 to 48 hours; Group II, age 3 to 6 days; Group III, age 7 to 30 days.

tained electrometrically spread over a smaller area of the pH scale than the indicator readings, i. e., shifts of pH toward neutrality or stronger acidity appeared to be less pronounced. Thus, with infants of Group I, all electrometric values fell in the range from pH 5.9 to 6.9, while the readings in Group II spread from pH 4.8 to 6.0.

No significant differences were noted when readings were compared for race or sex.

Comment

The development of skin pH changes during the newborn period is summarized in Figure 3, in which the results are classified, somewhat arbitrarily, into one of two pH ranges: (1) readings between pH 3.0 and 5.9, the normal range of skin acidity as established in children and adults, and (2) readings of and above pH 6.0, indicating diminished skin acidity. The percentage distribution of these two ranges of pH readings demonstrates the early onset of the physiologic processes by which skin acidity is maintained at a normal degree. In 46% of the infants of Group I, tested at the early age of 1 to 48 hours, normal pH values are already established. Among the infants 7 days of age and older, only 4% have not yet attained the range of normal acidity.

Unlike the decrease in acidity known to occur in well-defined skin areas during childhood and adult life, the uniformly low skin acidity found in many newborns cannot be explained as the result of either sweat stagnation or delivery of apocrine sweat. How do these "alkaline" values come about?

It is highly improbable that they are due to a physiologic immaturity of the acidifying mechanism. One should not speak of a neonatal function as being physiologically impaired unless there is evidence that the dysfunction is an attribute of almost every newborn infant. The duration of such physiologic insufficiencies usually exceeds two weeks, e. g., renal and hepatic insuffici-

ency. The observed changes in the skin pH of the newborn do not conform to such a pattern. First, diminished skin acidity was found to be a feature not common to all newborns. A considerable proportion of our infants had pH values within the normal range, i. e., below pH 6.0, already on the first or second day after birth. Furthermore, the occurrence of abnormally "alkaline" skin pH values is restricted mainly to the first three or four days; only in a few instances was the attainment of normal acidity found to be delayed beyond the sixth day of life.

We believe that the skin pH pattern observed during the newborn period is related to the presence of vernix caseosa. This greasy covering of the fetus, formed mainly by fatty degeneration of epidermal cells, has an average pH of 7.4. If a film of vernix is still present at the time and site of testing, the pH reading will be influenced by these remnants. Moreover, the newborn skin surface itself is in an abnormal state for some time, forming what may be called a "fixed layer" of vernix. Its pH is of similar range as that of the vernix. Varying degrees of superficial maceration and desquamation create surface conditions which prevent the establishment of physiologic acidification. This is why our readings taken after careful cleansing of the test site were as high as before removal of apparent remains of vernix. Eventually, with complete disintegration and absorption of dead cell material, the outer aspects of the skin assume normal quality and function; the surface pH shifts downward.

Our studies indicate that the rate of this process is subject to considerable individual variations. Some infants possess a completely stabilized skin surface, with a normal range in pH, when tested right after birth. Here, the process of restoration apparently was completed during fetal life. In many other newborns an abnormally "alkaline" skin reaction persists for about five days, linking the essential transformation and possibly its beginning to the early neonatal period. Whether acid or more alkaline pH values will prevail at the time of birth may well depend on the duration of pregnancy. If this is true, a significant difference should exist between the skin surface pH of premature and that of postmature babies at the time of birth, a question which is being investigated presently.

Likewise, further studies are warranted to explain the comparatively late appearance of normal pH values on the abdominal wall. Differences in the anatomic structure of different skin areas may play a role.

No attempt will be made here to relate our findings to the onset of sweat gland function. It should, however, be pointed out that apparently factors other than sweat are essential for the acidification of the skin surface.[6-9]

Summary

The relationship of skin pH to chronologic age was studied in 222 young infants.

During the first two days, 54% of the newborns showed abnormally "alkaline" skin pH values on all three sites tested; 46% had a markedly acid skin pH.

During the first week of life, there is a progressive increase in the percentage of newborns who have fully developed skin acidity. Infants 7 days of age and older rarely fail to have a normally acid skin pH.

The low skin acidity observed during the newborn period is most likely caused by the neutralizing influence of the vernix caseosa. It appears that the shift from more alkaline to acid pH values is directly related to the gradual transition to a normal skin surface.

There is no evidence in support of the view that the mechanism which effects skin acidity is not operating during early life.

Dr. F. Herrmann gave criticism, and Miss Leona Mandol performed the electrometric measurements.

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Conversion Hysteria in Childhood

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The frequency of conversion hysteria in children is impossible to estimate accurately, as the variability in the use of the diagnostic criteria is marked. It is, however, a rare condition. It is the feeling of the staff of the North Carolina Baptist Hospital Pediatric Service that the number of cases seen here is greater than that expected on the basis of the experience at other institutions.

One of the possible explanations for this apparently higher incidence is the predominantly rural culture of the referral area of this hospital. This area, in spite of the rather recent increase in industry, is still one of the last truly rural cultures in the nation. Families live in isolation or semi-isolation, with a strong patriarchal control. Folklore and superstition are integral and powerful parts of the culture. Modern agricultural methods are not as yet widespread. Sanitation, nutrition, education, and sophistication are still lacking, at least in any modern up-to-date manner, to rather significant portions of the populace of the area. It is not the economic backwardness but the cultural infantilism that seems to predispose to hysteria. The grand hysterical attacks of the earlier writers seldom occur now in urban populations, since society has matured and no longer allows uncontrolled emotional releases. Hysteria is a relatively poor term, since the lay connotation of wild excitement and emotionality in females is often carried over into the medical usage of the word. Furthermore, it denotes a specific organ, the uterus, which is rarely associated with the syndrome.

Conversion, on the other hand, is the very cornerstone of the present-day concept of the pathogenesis of this rather serious psychoneurosis of childhood and later life. In simple non-Freudian terms, the dynamism—conversion—is an unconscious expression in physical symptoms of emotional conflicts. It is this unconscious expression that differentiates conversion hysteria from malingering or hypochondriasis.

Conversion, in the Freudian concept, results when instinctive thoughts or wishes are unacceptable to the person and cannot be repressed strongly enough. There is then a displacement of them to a neutral part of the body and expression in somatic symptoms. Since it is felt that, for the most part, these instinctive wishes are genital in origin, conversion would not be expected to occur prior to the onset of genital primacy at 2 to 3 years of age. When it does occur, it represents a regressive tendency, to the pregenital situation of self-love.

It is not possible to cover the entire field of symptoms found in conversion hysteria. Table 1 lists the commoner forms seen.

One of the important differential points in conversion hysteria is that although the symptoms may closely simulate actual organic processes and may even, if long continued, lead to actual physical changes, such as disuse atrophy, contractures, trophic changes, and others, careful and repeated examination will show them to be simulations. They are generally bizarre and dramatic. The symptoms are absent during sleep. They seldom fall into anatomical or neurological structural units. In children, especially, the symptoms are inclined to be all-or-none reactions, i. e., no pain is felt,

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TABLE 1.—*Symptoms in Conversion Hysteria*

I. Somatic manifestations
  A. Sensory
    1. Touch
    2. Pain
    3. Temperature
    4. Kinesthesia
    5. Vision
    6. Hearing
    7. Taste
    8. Smell
  B. Motor
    1. Postures
    2. Tremors, choreiform movements
    3. Paralyses
    4. Astasia-abasia (paralytic, spastic, choreatic)
    5. Speech
  C. Visceral
    1. Hyperfunction of any system
    2. Hypofunction of any system
    3. Vasomotor manifestations
II. Episodic performances or states
  A. Prodromal stage
    1. Visual or auditory sensations
    2. Globus hystericus sensation
    3. Mood changes
    4. Pelvic, thoracic, or abdominal pain
  B. Epileptoid stage
    1. Rigidity
    2. Tonic or clonic convulsions (no injury sustained, no consciousness lost)
  C. Stage of posturing and grimacing (arc de cercle, rotating, kicking, and "clownism")
  D. Stage of affective attitudes (terror, rapture, love, hatred)
  E. Delirious stage (usually not followed by amnesia)
III. Fugues or twilight states
IV. Paralogia (the Ganser syndrome) (syndrome of approximate answers)
V. Dual or multiple personalities

TABLE 2.—*Age at Onset of Hysteria**

Age, Yr.	Cases, No.
4½	1
6	2
8	2
9	3
10	4
11	9
12	1
13	4
14	1

* Mean age, 9 years 8¾ months; median age, 11 years. There were 21 girls and 7 boys.

no movement is possible, and food is refused to the point of extreme inanition. In addition, the child's reaction to the symptom is often of great help. The hypochondriacal child worries about his symptoms and continues to complain of them in his effort to get attention and sympathy. The child who is malingering has to accentuate his suffering, although he may show ill-concealed pleasure is so doing, in order to continue to derive the attention he seeks. Children with conversions, on the other hand, are almost universally unconcerned in the face of severely crippling symptomatologies. The conversion is the end in itself. It has already solved the problem, and there is no longer any need for concern on the child's part.

In connection with this lack of affective response in children during conversions, it is of interest to mention some of the attributes of the hysterical personality. Much has been written about hereditary predisposition, the hysterical taint, and so forth; yet, at present, there is no real evidence that the predisposition is inherited. However, there seem to be a few characteristic traits that are found in the personality structures of most children who have conversion hysterias. Hysterical children are immature, have a need to be the center of attraction, display an assumed poise, are superficial, are subject to unmotivated mood swings, carry emotional expression to extremes, are great imitators, are very suggestible, are quick to form likes and dislikes, are inclined to make quick judgments, are generally happy in the presence of serious symptoms, and are unaware of any conflicts. In addition, it would appear that these children find it difficult to make normal emotional ties with their parents and must resort to a dramatic illness in an effort to control their environment and satisfy their egocentric inner needs.

The experience of the pediatric service of the North Carolina Baptist Hospital from November, 1943, until March, 1954, is summarized in Table 2. During this 10½-year period 28 of the hospitalized children were diagnosed as having conversion hysteria. During this same period there were approximately 10,935 cases admitted to the pediatric service.

The average age of our series was 9 years 8¾ months, with the median at 11 years. This is in keeping with the experience of others, who feel this syndrome is

TABLE 3.—*Choice of Symptom in Hysteria*

Symptoms	Cases, No.
Seizures	13
Astasia-Abasia	5
Dysphagia	4
Globus hystericus	4
Abdominal pain	4
Episodic states	3
Paresthesias or hypesthesias	2
Aphonia	1
Sternutations	1
Hyperventilation	1
Polydipsia-polyuria	1
Chronic invalidism	1

commonest in the preadolescent years. There were 21 girls and 7 boys, also an expected figure. The choice of symptom is outlined in Table 3. Nine of the patients showed polysymptomatic conversions. It is the usual experience to have the child pick one symptom and stay with it, and this is what the greater percentage in this series did.

To illustrate some of the difficulties encountered in making the diagnosis, there follow brief abstracts of two case histories.

Case 1.—A girl was admitted at the age of 11 years with the chief complaint of seizures of undetermined etiology. Her family history is of interest in that her parents were first cousins; the mother had had four children by a previous husband, three of whom lived out of the home. The patient was the oldest of four children in the present marriage. The family lived in utter squalor, with pigs literally sharing the living room. Her past history was essentially noncontributory. Her present illness began with acute nephritis two and one-half months prior to admission. She was hospitalized near her home for a week, improved, and was discharged home. There was an exacerbation of the nephritis, and she was rehospitalized. In a short while she was again discharged. After a third reinfection and exacerbation she was hospitalized and then discharged to a boarding home near the hospital. On the day of her final examination before going to her own home, and just before she was to be taken to the hospital for this examination, she fell to the floor in what was described as a fit. She was immediately hospitalized and was treated for the next month with a variety of sedatives and anticonvulsant medications. Ether anesthesia was the only method by which her seizures could be controlled. At the end of the month she was transferred to the pediatric service of the North Carolina Baptist Hospital for further evaluation. On admission she was having bizarre groping movements of the arms; her eyes deviated upwards and to the left. She became delirious on the ward, spoke of seeing her father's head in a gully, a baby sitting on the head of her bed, and expressed a fear that the water pipes would fall on her. She refused to eat and had to be given intravenous feedings. Routine laboratory studies were within normal limits. An electroencephalogram was reported as follows: "This tracing shows no abnormality and it is considered within normal limits." Calm handling by the medical and nursing staffs with firm but gentle insistence that intravenous feedings would be continued until she began to eat quieted her, and she began to take food on her third hospital day. At the same time her seizures ceased, although no medication had been given.

From this point on, rapport was built up through frequent interviews. A boarding home was found, and the patient was followed for the next six months in the guidance clinic. At the end of this time she was able to go to her own home and was doing well in the sixth grade, although her intelligence quotient was only 67. There was no recurrence of the symptoms during a period of 24 months she was under observation.

Case 2.—A girl was admitted at the age of 9 years. Family and past history were not of any significance. Her present illness started with abdominal pain 21 months prior to admission, without relief of her symptoms. A complete urological work-up including cystoscopy was done 18 months prior to admission, but there was no relief of her symptoms. Tonsillectomy and adenoidectomy were performed 10 months prior to admission, but the patient continued to have abdominal pain. Nine months prior to admission, the patient was severely ill with varicella for one week. From then until admission she was unable to walk. Eight months prior to admission she began to have regular daily periods of hyperventilation, at first between 8 and 9 a. m., later between 4 and 5 p. m. She was seen in the outpatient department of the North Carolina Baptist Hospital for the five months prior to her admission, and extensive investigation revealed no organic cause for her symptoms. The patient remained in this hospital for 52 days, at the end of which time organic neurological illness had been ruled out. With the aid of psychotherapy and physical therapy she became able to walk and the abdominal pain disappeared. She remained well and active and made a satisfactory adjustment to the second grade, two years behind the grade in which her chronological age would have placed her.

These cases are picked because they represent the two symptoms most frequently seen in this series and demonstrate the lengths to which attempts to establish organic pathology may go before the psychiatric aspects of the picture are clarified and the diagnosis made.

One word of warning, though, may be found in one case of an 11-year-old boy who was not included in this series. Repeated investigations of his neurologic system and gastrointestinal tract failed to reveal evidence of organic disease which might have caused his vomiting and dysphagia. He was treated psychotherapeutically for six months without success. At

that time reinvestigation revealed a pontine tumor. It is important to add, retrospectively, that this child had few of the factors which have been so startling in our hysterical patients. The most striking difference was that this boy's symptoms did bother him.

The treatment of conversion hysteria is not a simple matter. There are, however, two underlying principles that must be considered. The first is that the symptoms must be reconverted before psychotherapy can be effective. That is, you cannot obtain rapport with a child having seizures. You have to use, in general, a firm, nondramatic, nonpunitive approach. If the patient sees that you are no longer impressed or upset by his productions, his own satisfaction with the excellence of his act is damaged. "Shock" methods will work, but they are not as helpful as less dramatic approaches.

After the patient is accessible, a gentle and slow approach with him to the underlying problems and help in solving these is the only way in which a permanency of cure can be established.

Comment and Summary

It is to be recognized that the cases presented in this study represent those coded as severely ill or incapacitated with their symptoms. It would be most difficult to establish accurately the number of children seen with less severe complaints, but ones that could conceivably be diagnosed as an organic symptom resulting from emotional tension. The cases included here are those in whom the severity of the illness and the patient's unconcern made a positive diagnosis of conversion hysteria evident.

In summary, then, the rather rare psychoneurosis, conversion hysteria, has been seen with greater than the expected frequency at the North Carolina Baptist Hospital. The predominantly rural culture of the state, with the tendency toward isolation of families and strong patriarchal control, may play a role in this.

The major diagnostic criteria of the syndrome are discussed. Twenty-eight cases are summarized as to age, sex, and choice of symptom. Two cases are presented briefly.

It is hoped that reaccentuation of this problem will heighten the index of suspicion of pediatricians so that the diagnosis will come to their minds whenever they see a child with an acute, bizarre, dramatic illness, to which the child reacts with relative unconcern.

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Congenital Stenosis of the Aortic and Pulmonary Valvular Areas of the Heart

Indications for Early Surgical Relief

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The grave prognostic import of congestive heart failure incident to isolated pulmonic stenosis or to aortic or subaortic stenosis is well known to those interested in the field of cardiology. In fact, it is not an extreme rarity for sudden death to occur even in the absence of recognizable evidence of cardiac failure. Awareness of these hazards has resulted in a drastic lowering of the optimal age at which special diagnostic procedures and definitive surgery are undertaken. Because this recent swing of the pendulum has received little attention in the pediatric literature, it is felt that a discussion of this problem may be of value. The following case reports have been selected from the patients seen in our pediatric cardiac clinic to illustrate the importance of early diagnosis and of prompt surgical relief in patients with advanced degrees of obstruction.

Report of Cases

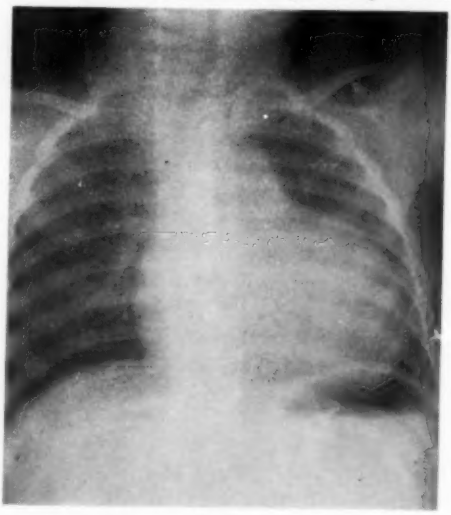
CASE 1.—A 15-month-old Caucasian girl was admitted to the U. C. L. A. Medical Center for evaluation of a heart murmur which was first heard at the time of her birth. Cyanosis of the hands and feet noticed at one year of age had become progressively more pronounced up to the date of admission. There were no other symptoms referable to the cardiovascular system.

Physical Examination.—Physical examination revealed a pale infant with cyanosis of the extremities and clubbing of the fingers and toes. Blood pressure determined by the flush technique was 64 mm. Hg in the right arm and 62 mm. in the right leg. A Grade 3 harsh systolic murmur was audible over the entire precordium, being maximal at the second interspace to the left of the sternum. An associated systolic thrill was palpable over the pulmonic area.

Laboratory Data.—The erythrocytes numbered 8,630,000 per cubic millimeter, with 15.0 gm. per 100 cc. of hemoglobin, and the hematocrit value was 52%. Teleroentgenograms disclosed a fairly marked degree of cardiomegaly, with prominence of both the right and the left ventricle. The pulmonary vessels were small, as was the waist of the heart. The lung fields were clear, and the appearance was consistent with that of a complicated tetralogy of Fallot (Fig. 1). The electrocardiogram showed evidence of extreme right ventricular hypertrophy.

Course.—A right heart catheterization was performed two days after admission to the hospital.

Fig. 1 (Case 1).—Roentgenogram, showing marked cardiomegaly and small pulmonary vessels.



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The systolic pressure in the main pulmonary artery was 9 mm. Hg, and that in the right ventricle, 169 mm. Hg. Oxygen saturations determined on samples of blood removed from the chambers of the right side of the heart and from the cavae showed no evidence of a left-to-right shunt, but the saturations were found to be extremely low, ranging from 31% to 42% (probably owing to a low cardiac output).

Since the catheterization data established the diagnosis of severe pulmonic stenosis with an intact ventricular septum, the patient was scheduled for operative repair three days later. While she was awaiting surgery, however, cardiac arrest suddenly occurred. A thoracotomy and emergency pulmonary valvulotomy by Dr. Rodney Smith were of no avail.

Autopsy Findings.—The heart was greatly enlarged, weighing 95 gm. (normal weight about 40 gm.). The epicardium showed a moderate number of ecchymotic areas. A small recently sutured incision lay in the pulmonary conus. The right atrium and ventricle were markedly hypertrophied and moderately dilated. The foramen ovale was obliquely patent anatomically, with a well-formed valve. The tricuspid valve was thin and competent. The trabeculae of the right ventricle, as well as the wall, were markedly hypertrophied. The basal portion of the wall was 10 mm. thick, compared with 7 mm. for the smaller left ventricle. The pulmonary valve was extremely stenotic. The leaflets were thick and fused to form a cone-shaped tube projecting beyond the three poorly developed commissures into the pulmonary artery. The valve had been ruptured along one radius to its base. Before rupture the diameter of the lumen appeared to have been only 2 mm. The pulmonary artery had a thin dilated wall measuring 4.0 cm. in circumference, compared with 3.0 cm. for the aorta. The ductus arteriosus was obliterated. The left atrium and ventricle were slightly dilated, but they were considerably smaller than their counterparts on the right. The mitral and aortic valves were thin and competent. The coronary arteries were normal in size and distribution. The valve ring circumferences were as follows: tricuspid, 4.5 cm.; mitral, 4.8 cm.; aortic, 2.9 cm.

The liver, spleen, and kidneys weighed somewhat less than the averages for this age. The left lung showed marked atelectasis. The jejunum contained a small amount of blood, and there were petechial hemorrhages in the mucosa. Microscopic examination revealed edema and focal hemorrhage in the lungs. Necrotic nuclear fragments were found in the germinal centers of lymphoid tissue.

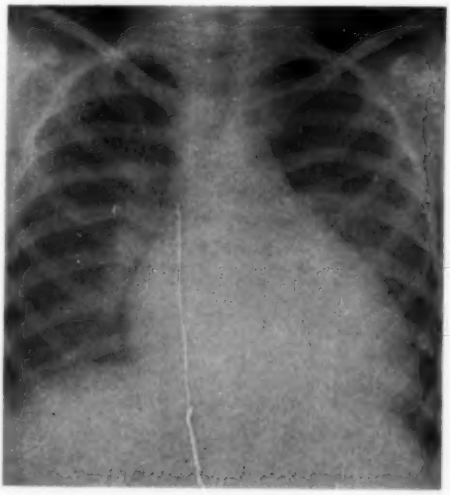
The marked hypertrophy of the right ventricle was probably responsible for rounding and lifting of the apex of the heart as seen in the x-ray. Atelectasis, mucosal intestinal hemorrhages, and necrosis in germinal centers are common findings in patients with cardiac disease dying postoperatively.

CASE 2.—A 10-year-old Caucasian girl was admitted to the U. C. L. A. Medical Center because of congestive heart failure. Approximately three weeks prior to admission she had been hospitalized for treatment of a supraventricular tachycardia which responded well to digitalis. The parents had been aware for a number of years that the child had aortic stenosis and a Wolff-Parkinson-White syndrome. She had been under the observation of a cardiologist since early infancy. A cardiac murmur had been present since birth, but there had not been any cyanosis or signs of exercise intolerance. The parents observed, however, that for one week prior to her present admission she had developed moderate dyspnea and orthopnea.

Physical Examination.—Examination disclosed moderate dyspnea, slight cyanosis of the lips and nailbeds, 2+ pretibial edema, and moderate hepatomegaly. The blood pressure in the right arm was 80/60 mm. Hg, and that in the right leg, 92/70 mm. A Grade 3 harsh systolic murmur was audible over the entire precordium but maximal at the second and third interspaces to the right of the sternum. The second aortic sound was inaudible.

Laboratory Data.—The erythrocytes numbered 4,700,000 per cubic millimeter, and the hemoglobin was 15.3 gm. per 100 cc. Teleroentgenograms revealed a fairly marked cardiomegaly predomi-

Fig. 2 (Case 2).—Roentgenogram, showing marked cardiomegaly involving predominantly the left ventricle.



nantly of the left ventricular type and consistent with the diagnosis of aortic or subaortic stenosis (Fig. 2). An electrocardiogram showed evidence of a Wolff-Parkinson-White syndrome, and, because of this, specific chamber hypertrophy could not be assessed.

Course.—The patient responded well to digitalization and was scheduled for a right heart catheterization. On the day of catheterization a bigeminal rhythm was observed prior to initiation of the study. At the start of the procedure, when the catheter tip was inserted into the right atrium, ventricular tachycardia was observed on the electrocardiogram. The catheter was immediately withdrawn to the iliac vein, and 50 mg. of 10% procainamide (Pronestyl) hydrochloride was injected into the catheter, resulting in a prompt reappearance of the bigeminal rhythm. Because of the extreme irritability of the heart, it was decided to abandon the procedure in favor of angiocardiography. However, before this could be accomplished, cardiac arrest occurred, and it was found necessary to perform a thoracotomy and institute cardiac massage. A partial aortic infundibulectomy was performed while the heart was massaged, but, despite all efforts, the patient died.

Autopsy Findings.—The heart was markedly enlarged, weighing 400 gm. (normal weight about 116 gm.). The epicardium was hemorrhagic over most of the left ventricle. A recent surgical incision below the aortic valve was closed with sutures. All chambers of the heart were dilated, especially the left atrium and ventricle. The foramen ovale was closed, and the tissues were fused. The tricuspid valve ring measured 8.8 cm.; the pulmonic, 5.5 cm., and the mitral, 8.3 cm. These valves were well formed and competent. The right ventricle was moderately hypertrophied, and the myocardium was of good color. The ductus arteriosus was obliterated. The left atrium and ventricle showed marked hypertrophy. The left ventricular wall was 15 mm. thick, and the right, 7 mm. The endocardium of the left ventricle was irregularly thickened, and the mottling of myocardial hemorrhage could be seen through it. Many areas of light gray fibrous tissue and hemorrhage were scattered throughout the myocardium of the left ventricle and interventricular septum, except in the posterior portion of each. These areas lay in the distribution of the left coronary artery. The right coronary artery supplied the posterior portion of the interventricular septum and left ventricle. Just beneath the aortic valve was a diaphragm formed by a ring of fibrous tissue surrounding a hole with a diameter of 7 mm. The septum membranaceum could not be identified. The cusps of the aortic valve were thick, and the commissures were fused. The aortic intima was also thick in the posterior and left anterior aortic sinuses. In the latter this process had narrowed the mouth of the left coronary artery to the extent that the lumen was pinpoint in size. The intima of the right anterior aortic sinus was thin, and the mouth of the right coronary artery was wide (Fig. 3). The coronary arteries distal to the mouths showed no lesion.

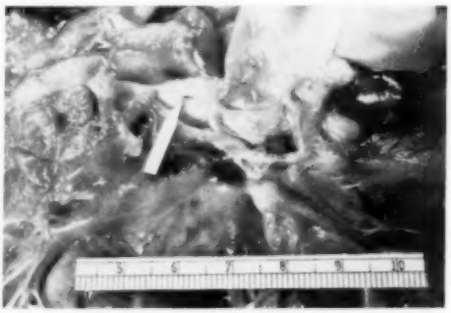


Fig. 3 (Case 2).—Photograph of the aortic area. The diaphragm producing the subaortic stenosis was separated from that part of its attachment at the base of the right anterior aortic leaflet during cardiac massage. The dark rectangular block lies in the original lumen. The white arrow at the right points to the stenotic mouth of the left coronary artery. The white arrow at the left points to the uninvolved mouth of the right coronary artery. (The photograph was taken by Dr. Dean L. Moyer.)

The lungs exuded a large amount of yellow frothy fluid from the cut surface. The liver and spleen appeared hyperemic. The spleen was large, weighing 180 gm., but the liver showed little, if any, increase in weight, weighing 780 gm.

Microscopically the myocardium from the left ventricle showed small scattered areas of fibrosis replacing muscle fibers. The scars contained loose collagen fibers which had not yet hyalinized. An occasional macrophage containing hemosiderin was seen, and foci of fresh hemorrhage were present. Most of the alveoli in the lung contained the proteinaceous deposit of edema fluid and a moderate number of mononuclear cells, some with phagocytosed lipid. Large areas of fresh hemorrhage were also present. The splenic pulp was hyperemic. The liver cells showed slight atrophy and a few fat droplets. The sinusoids were only slightly hyperemic. Lymphoid follicles contained necrotic nuclear fragments.

The histologic appearance of the small foci of scarring in the myocardium suggests that focal infarctions and cardiac failure could account for the episode of tachycardia for which the patient was hospitalized approximately four weeks before death. The stenosis of the ostium of the left coronary artery probably developed gradually, facilitating a collateral coronary circulation, since

more abrupt occlusion would likely have produced more extensive damage. The clinical and autopsy findings suggest that left-sided heart failure probably developed terminally. Although no thickening of the walls of the pulmonary arteries or arterioles was noted, the hypertrophy of the right ventricle indicates that there must have been an increased pressure in the pulmonary arterial system. Although reduction of pulmonary blood flow because of the subaortic stenosis might delay arterial hypertrophy, a greater factor would seem to be the probability that left ventricular failure became prominent only relatively late in the life span of the patient.

CASE 3.—A Caucasian girl was first seen at 8 months of age. The parents had been told at the time of her birth that she had a heart murmur. The only other sign or symptom referable to the cardiovascular system was cyanosis of the extremities, which had developed within the preceding two weeks.

Physical Examination.—Examination revealed a well-nourished child who was 66 cm. tall and weighed 7400 gm. There was generalized cyanosis, which was most prominent about the nailbeds. The blood pressure determined by the flush technique was 68 mm. Hg in the right arm and 74 mm. in the right leg. A Grade 3 systolic murmur was audible over the entire precordium but maximal at the second and third interspaces to the left of the sternum. There was no associated thrill. The second pulmonic sound was single and of diminished intensity.

Laboratory Data.—The erythrocytes numbered 6,510,000 per cubic millimeter, with 15.75 gm. per 100 cc. of hemoglobin, and the hematocrit value was 52%. Teleroentgenograms revealed only minimal enlargement of the left border of the heart and some hypovascularity of the lung fields (Fig. 4A). The electrocardiogram indicated right ventricular hypertrophy.

Course.—Clinical observations and laboratory studies indicated that the diagnosis was tetralogy of Fallot. The patient was observed by her local physician, who reported that her cyanosis was becoming more pronounced and that the hematocrit value was increasing. At one year of age the erythrocytes had increased to 9,000,000 per cubic millimeter; the hemoglobin, to 22 gm. per 100 cc., and the hematocrit value, to 60%. She was, accordingly, admitted to the U. C. L. A. Medical Center for definitive studies and possible surgery. At that time it was observed that the murmur had decreased from Grade 3 to Grade 1 in intensity.

Right heart catheterization was performed and revealed a systolic pressure of 192 mm. Hg in the right ventricle. The main pulmonary artery could not be entered. Oxygen saturations determined on blood samples removed from the chambers of the right side of the heart and from the cavae indicated that there was no left-to-right shunt, but the low range of 25% to 48% saturation suggested a very low cardiac output. With the catheter tip in the right ventricle, 10 cc. of 50% sodium diprotrizoate (Miokon Sodium) was injected at 5 kg. per square centimeter pressure. Films were taken

Fig. 4A (Case 3).—Roentgenogram, showing only slight cardiomegaly and some hypovascularity of the lung fields.

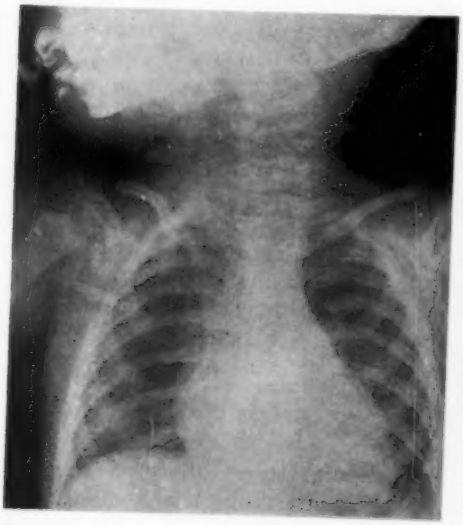


Fig. 4B (Case 3).—Selective angiocardiogram, showing catheter in right ventricle and opaque material filling the right ventricle and pulmonary artery. Note jet stream produced by stenotic pulmonary valve.

in the posteroanterior and lateral positions, 36 frames being made in each plane over a period of 10 seconds. As is readily seen in Fig. 4B, the stenotic pulmonary valve was clearly visualized. Because of the extremely high pressure in the right ventricle and the low cardiac output, it was decided to perform emergency surgery.

Surgical Findings.—On the evening of the day of the catheterization, after satisfactory induction of anesthesia, a left submammary incision was made, and the chest was entered through the third interspace. Upon exposure of the heart, it was observed that the myocardium was extremely cyanotic. It was felt unwise to delay the valvulotomy to determine pressures, and, consequently, two 000 nonabsorbable surgical (silk) stay sutures were placed in the wall of the right ventricle. A stab wound was then made, and a probe was passed up the pulmonary outflow tract, and the valve was palpated. The probe could not be passed beyond the valve. The Brock knife was then inserted through the valve, and within 30 seconds the myocardium became much less cyanotic. The pulmonary artery seemed to have a better pressure following the valvulotomy. This was confirmed by direct systolic pressure measurements of 50 mm. Hg in the right ventricle and 30 mm. Hg in the pulmonary artery.

Postoperative Course.—The postoperative course was uneventful, and the patient was discharged from the hospital. Five months later she was asymptomatic, and there was no visible cyanosis.

Comment

The pulmonic lesion referred to in the present discussion is severe valvular stenosis with an intact ventricular septum with or without a right-to-left atrial shunt. This type of lesion possesses many features in common with severe stenotic lesions at or below the aortic valve. Infundibular pulmonic stenosis is not considered here, since our experience is in agreement with the contention of others that this rarely occurs as an isolated lesion.[1-4] It should be mentioned, however, that all investigators do not adhere to this point of view.[5-7]

Physiologic Considerations.—In the absence of an interventricular septal defect to act as an escape valve, a severe stenotic lesion at the outflow tract of either ventricle places a great burden on the chamber itself. With pronounced obstruction, the cardiac output tends to be low and fixed. Regardless of which ventricle is primarily affected, the end-result is reduced systemic and coronary flow. This accounts at least in part for features such as a small peripheral pulse, chest pain, syncope, myocardial insufficiency, ventricular failure, and sudden death.

Diagnosis.—Early recognition is of the utmost importance. A detailed description of the pertinent clinical features, however, is not within the scope of this paper. For such a description, the reader is referred to the excellent works of Abrahams and Wood [8] and of Downing.[9] The murmur in both conditions is characteristically loud and harsh and systolic in time. It is widely distributed but is usually maximal in the second interspace to the left of the sternum with pulmonic stenosis and in the second interspace to the right of the sternum with aortic or subaortic stenosis. A systolic thrill is commonly present and in the case of aortic or subaortic stenosis may accompany the murmur up the neck vessels. With severe pulmonic stenosis the second pulmonic sound is usually single and either diminished in intensity or completely absent. Visible cyanosis may appear at any time with severe stenosis of the pulmonary valve, and, although usually of peripheral origin, it may on occasion be of central origin. When of central origin, it results from a right-to-left shunt through an atrial septal defect or foramen ovale. Clubbing and polycythemia may then be pronounced, and differentiation from Fallot's tetralogy may be difficult. Roentgenographic and electrocardiographic studies show evidence of enlargement of the left side of the heart with severe aortic or subaortic stenosis and of the right side with advanced valvular pulmonic stenosis. In the latter condition the lung fields are hypovascular and poststenotic dilatation of the main pulmonary artery can be demonstrated in the roentgenogram.

Indications for Special Diagnostic Studies.

In general, the recognition of severe degrees of the malformations under consid-

eration is not difficult, but in milder forms the diagnosis often cannot be established clinically with any degree of certainty. A definitive diagnosis of aortic or subaortic stenosis, as well as estimation of severity, however, can usually be made from data obtained by routine studies and, when necessary, by exclusion of certain other anomalies by right heart catheterization. We have not found it necessary, as yet, to employ left heart catheterization as is currently practiced in some laboratories. The diagnosis of pulmonic stenosis and the severity of this lesion can generally be established with certainty from data obtained by routine studies and by right heart catheterization. A gradient in the systolic pressure from the pulmonary artery to the ventricle is pathognomonic of this condition, and if the systolic pressure is 75 mm. Hg or over the degree of obstruction is probably severe. In those rare instances in which the pulmonary artery cannot be entered, selective angiocardiography may be performed by injecting an opaque dye through the catheter into the right ventricle. This not only demonstrates the presence of the lesion but also outlines its location and extent (Fig. 4B).

The indications for right heart catheterization in suspected cases of pulmonic stenosis are signs of diminished exercise tolerance or abnormalities of the electrocardiogram or roentgenogram. The age, size, or weight of the patient should not influence one's decision to obtain definitive studies. When the indications exist, special diagnostic procedures should be performed as readily as one does a spinal puncture or subdural aspiration in a small infant. Surgeons have conclusively demonstrated that with few exceptions infants tolerate surgical procedures as well as do older children. This has also been our experience with respect to cardiac catheterization. In fact, a policy of watchful waiting may be far more hazardous than one of intensive diagnostic study including cardiac catheterization and selective angiocardiography. We do not mean to imply, however, that such procedures are entirely without risk. In certain patients, as in Case 2, hazards may indeed be extremely great. Yet, had these hazards been chanced earlier in the course of her illness the final outcome might have been altered.

Indications for Surgery.—Indications for operative relief of aortic or subaortic stenosis have not, as yet, been clearly delineated. With accumulating experience it is rapidly becoming apparent that the risk of sudden death or cardiac decompensation is not insignificant.[10,11] For this reason, our present policy is to perform surgery at a relatively early age.

It is our feeling that any child with aortic or subaortic stenosis should have the benefit of surgery, regardless of his age, if he has a history of syncope or exercise intolerance or has pronounced cardiac enlargement as determined by electrocardiographic or roentgenographic studies. If cardiac failure is imminent, surgery should be performed as an emergency procedure. If cardiac failure has already occurred, surgery should be performed after an adequate trial of digitalization.

The indications for operative relief of pulmonic stenosis have also not been accurately defined. The attitude in many centers is to perform surgery if the systolic pressure in the right ventricle is 50 to 100 mm. Hg or over.[6,12-16] It is our present policy to recommend surgery without consideration of the age of the patient if he shows signs of exercise intolerance, if the systolic pressure in the right ventricle is 75 mm. Hg. or more, or if cardiac failure threatens. Of particular importance is the clinical observation of a murmur which diminishes in intensity with continued observation (see Case 3), since this is invariably the result of a decreasing cardiac output and indicates that right ventricular failure is imminent. Cases 1 and 3 support the contention that, in instances such as this, surgery should be performed as an emergency procedure.

Summary

The case histories of two children with severe valvular pulmonic stenosis and one with pronounced subaortic stenosis are presented. Two of the children died, one while hospitalized and awaiting surgery. The third, an infant with pulmonic stenosis, recovered after emergency surgery. The importance of and the indications for early definitive diagnosis and treatment are discussed. In selected cases this must be of an emergency nature.

Addendum

In the interim between the preparation of this paper and Nov. 21, 1957, we have encountered one additional case of a 12-month-old male infant with pure pulmonic stenosis who had cyanosis since the early neonatal period. A clinical diagnosis of tetralogy of Fallot had been made elsewhere and the patient had been observed by a cardiologist since birth. The true nature of the abnormality was established by right heart catheterization and selective angiocardiography, the pressure in the right ventricle being 138/0 mm. Hg. Operative repair was performed by Dr. James V. Maloney Jr., with excellent results.

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Case Reports

Histiocytoma of the Bronchus

Report of a Case in a Six-Year-Old Child

TALCOTT BATES, M.D., and OSMAN H. HULL, M.D., Monterey, Calif.

Primary tumors of the bronchus in children are rare. The majority of these are adenomas,[1-8] although cases of papilloma,[9] myoblastoma,[10] fibrosarcoma,[11] and adenocarcinoma[12-14] have been reported.* We have been unable to find in the literature a description of a bronchial tumor of the type to be presented. Stout[15] has seen one similar tumor in the bronchus of a 46-year-old woman.

Report of Case

A six-year-old white boy was first seen on Jan. 3, 1950. He had had pneumonia three weeks previously, and he complained of persistent cough.

The past history was significant in that he had had pneumonia at the age of 4 years. He had recovered completely from this illness and had no respiratory or other illnesses until the onset of his present illness.

Physical examination showed him to be alert and well-nourished; weight was 25.8 kg.; height, 116 cm. The skin and mucous membranes were clear. Both lung fields contained scattered medium moist rales. There were no other abnormal physical findings. Blood study showed hemoglobin, 14.0 gm. per 100 cc.; WBC, 12,300, with a normal distribution of cells. Fluoroscopic examination showed opacity of the lower portion of the right lower lobe. A diagnosis of pneumonia, etiology undetermined, was made.

He was treated with bed rest and chlortetracycline. The cough cleared, and on Jan. 14, 1950, he appeared entirely well. Reexamination by fluoroscope however, showed a narrow area of persistent opacity lateral to the right cardiac border.

On Feb. 22, 1950, he had a paroxysm of coughing after eating. The cough persisted, and when examined two days later he had a temperature of 104 F (40 C), red bulging tympanic membranes bilaterally, and dullness at the right lung base. There were no rales or other abnormal physical findings. Bed rest and chlortetracycline therapy were resumed.

Following eight days of treatment, with symptoms and signs unchanged, roentgen examination revealed an apparent atelectasis of the right middle lobe of the lung, possible atelectasis of the anterior segment of the right lower lobe, compensatory emphysema in the remainder of the right lung field, and pleural effusion or thickened pleura at the right base. A tuberculin patch test showed no reaction. The impression was that an occlusion of the right main stem bronchus existed and that this was due to either a bronchial tumor or a foreign body. Bronchoscopy was advised.

Reexamination in another hospital showed similar findings plus a negative reaction to O. T. 1:100. Bronchoscopy showed a tumor completely obstructing the lower right main bronchus, with the base on the medial wall. The tumor was firm and slightly lobulated and bled slightly when the largest portion was removed with a forceps.

The preliminary report of the pathologist stated that the tumor was "anaplastic and infiltrative." A subsequent report stated, "bronchus infiltrated by masses of large reticulo-endothelial cells, suggestive of endothelioma or reticulo-endotheliosis."

Bone marrow studies showed no reticuloendothelial infiltration. A skull and long bone roentgen survey showed no abnormalities. Roentgen studies with barium showed no esophageal denting.

On March 17, 1950, the patient was operated upon. About 40 cc. of straw-colored fluid was found in the right pleural cavity. The entire lung was well aerated. No tumor could be palpated in the lung, bronchi, or mediastinum. The right main stem bronchus was opened, and a small tumor was seen 1 cm. below the carina. Adjacent peribronchial thickening and inflammation was noted. Examination of a frozen section of tissue from the tumor resulted in a diagnosis of "anaplastic squamous cell carcinoma of the lung." A right pneumonectomy was done. The patient tolerated the operation well.

Pathology.—The bronchoscopy biopsy sections (Fig. 1) show tissue which is cellular and has a minimum of fibrous stroma. The tumor cells tend to form rounded or slightly irregular groups out-

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*Case reports referred to in the references cited have been omitted from the list of references.

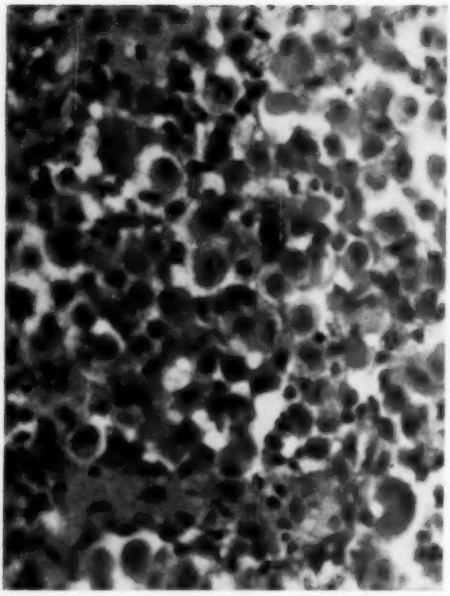


Fig. 1.—Tumor composed of histiocytes arranged in groups.

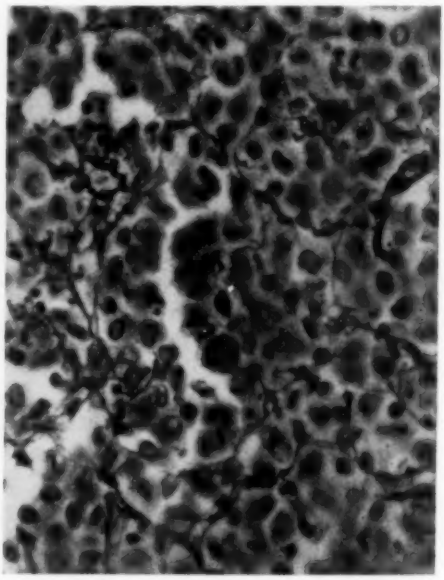
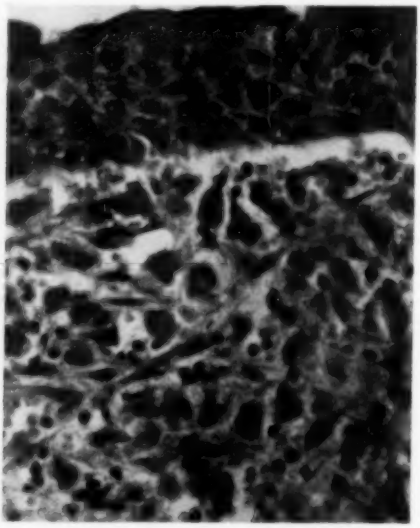


Fig. 2.—Reticulum pattern, showing arrangement in groups and no reticulin production by individual cells.

lined by delicate fibrous trabeculae containing capillary channels. Individual cells are moderately large, rounded, or indistinctly polyhedral and have an abundance of finely granular acidophilic cytoplasm. Cytoplasmic borders are slightly ragged. Under reduced light, cytoplasmic shreds between separated cells have the appearance of intercellular bridges. Nuclei are central or slightly eccentric, oval to slightly lobulated, and vary only moderately in size. The nuclear membrane is thin but distinct and is frequently indented or folded. A single

Fig. 3.—Edge of the tumor, showing ulceration and extension through the thickness of the bronchial wall.

Fig. 4.—Squamous metaplasia of the bronchial mucosa. The edge of the histiocytoma is seen in the submucosa.



small nucleolus is centrally placed, and chromatin is evenly distributed as a delicate network. Mitotic figures are rare. Lymphocytes, plasma cells, and occasional polymorphonuclear cells can be seen accompanying the fibrous trabeculae.

Reticulum stains (Fig. 2) show reticulum fibers which are moderately heavy and numerous along vascular walls. These give off thin branching strands which pass between some cells. Individual tumor cells are not producing reticulin.

The sections from the resected bronchus (Figs. 3 and 4) show no tumor.

The main portion of the tumor is composed of cells identical to those in the biopsy specimen. The borders of the involved area are moderately distinct; they extend beneath intact mucosa, beyond normal bronchial cartilage rings, and to the outer limits of the bronchial wall. Bronchial glands are surrounded by tumor cells and in the center of the lesion are atrophic or absent. Vascular channels and nerves show no unusual changes. The deeper layers of the bronchial wall show increased fibrous connective tissue with diffuse infiltrations of lymphocytes and plasma cells. Peribronchial lymph nodes show moderate reactive hyperplasia but no cells similar to those in the tumor.

Course.—In subsequent years the patient had difficulty with frequent respiratory infections, and his physical activities were somewhat limited. On July 17, 1955, after a fulminating pneumonia, he died.

Necropsy.—Necropsy showed a boy 154 cm. tall and weighing an estimated 45 kg. The heart weighed 230 gm., with hypertrophy and dilatation of the right ventricle. The trachea was deviated to the right. The stump of the right main stem bronchus showed no recognizable lesions. The bronchi to the left lung were dilated. The left lung weighed 960 gm. and was very voluminous, extending into the right thoracic cavity. Crepitation was markedly decreased. There were small areas of induration in the parenchyma, the largest not more than 1 cm. in diameter. In the bronchi were multiple gray-tan plugs which appeared to completely obstruct the bronchi to both lobes at a level of 0.5 to 0.6 cm. diameter. There was no evidence of tumor.

A microscopic examination of the lung showed focal areas of bronchopneumonia. The bronchial submucosa was infiltrated by many lymphocytes and plasma cells and showed some fibrosis. Multiple sections of the stump of the right bronchus and of the peribronchial lymph nodes showed no evidence of tumor. The remainder of the necropsy findings were not remarkable.

Necropsy diagnosis was "Acute fulminating bronchopneumonia. Right pneumonectomy."

Comment

The tumor in this case is composed of cells which histologically are histiocytes. Histiocytes or fixed macrophages are cells found in the loose connective tissues of the body that are capable of taking up particulate matter and storing foreign substances brought to them in colloidal solution. Under the stimulus of inflammation new histiocytes develop by mitotic division of the preexisting macrophages, by direct assumption of phagocytic activity by mesenchymal cells, and by hypertrophy and development of lymphocytes and monocytes. Cells of histiocyte type have been described in hemangiomas of lung,[16] but these were not the principle structure of the lesion presented. Comparison of these cells with those of plasma-cell tumors,[17-19] myoblastomas,[10,20] and bronchial tumors of epithelial origin shows no close similarity. Neither do these cells resemble those of any of the leukemic infiltrates or the cells of a xanthoma.[21]

Stout,[15] in reviewing the slides in this case, stated, "I was struck by the resemblance of the cells . . . to tumors which I like to call histiocytomas in the skin. These differ from the ordinary fibrous xanthomas by the fact that their cells contain no lipids, they grow in solid masses without any reticulin fibers among them, and they are benign. Moreover, they differ from the ordinary reticulo-endothelioses by the fact that they are solitary and are not associated with any disease in the bone marrow or other organs." Stewart,[22] who also reviewed the sections in this case, states, "on the microscopic evidence alone I would concur with Dr. Stout's diagnosis of histiocytoma. The structure in no way resembles plasma cell lesions of the lung that I have seen."

We consider this tumor to be benign, as it is only slightly due to local proliferation and principally due to an accumulation of cells contributed by the blood stream.

Summary

A case of histiocytoma of the bronchus is reported. We consider this tumor to be benign. We find no previous report of a histiocytoma of the bronchus in childhood.

920 Cass St.

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Progress in Pediatrics

Chronic Vitamin A Intoxication

Report of a Case in an Older Child and Review of the Literature

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Poisoning due to prolonged ingestion of high doses of vitimain A (hypervitaminosis A) in children 3 years of age and younger was first described more than a decade ago. Several cases have also been reported in adults. Recently two children beyond 3 years of age with chronic vitamin A intoxication have been reported from England. The following report describes an additional case in an older child.

Report of Case

A 14-year-old white girl * was admitted to The Children's Hospital on Sept. 11, 1956, with the chief complaint of leg pain of five weeks' duration. Two years prior to admission the patient developed superficial, nonpitting acne vulgaris, for which, 10 months prior to admission, 200,000 units of vitamin A daily had been prescribed by a dermatologist. Two months prior to admission she had had her last normal menstrual period, succeeding ones being at the normal interval but scanty and of one day's duration. About the same time, the patient noted scaling and cracking of her lips and fissuring at the corners of her mouth, for which she used a number of salves without success. Five weeks before admission she began complaining of dull constant pain in her legs, particularly about the knees, aggravated by activity. At this time she was seen by her private physician, who directed that vitamin A be discontinued. This advice was not heeded by the patient, unbeknownst to either her family or the physician. In the month prior to admission leg pain worsened. She walked with a noticeable limp, favoring her left leg, and was unable to continue in gym activities. She observed that her scalp hair became dry in texture and fell out in large quantities with brushing. She also developed a maculopapular eruption on her trunk and desquamation of palms and soles. The family observed during this period that she manifested increasing irritability, but there were no specific symptoms of central nervous system involvement. No bleeding or bruising was noted. Appetite remained good, although the patient was on a self-imposed, rather rigid, diet because of the acne.

Family History.—Noncontributory.

Past History.—Essentially unremarkable. Menarche occurred two and one-half years prior to admission, and menstrual periods had been normal up to the present illness.

Physical Examination.—Weight, 54 kg.; height, 169 cm.; blood pressure, 130/70. Skin: The face (Fig. 1) was the site of superficial nonpitting acne vulgaris and milia. The lips were scaled and cracked, and there were fissures at the corners of the mouth. Over the trunk and to a less degree on the extremities was a fine discrete light tan nonpruritic papular eruption. The skin was dry, and the skin of the palms and soles (Fig. 2) was desquamating in sheets. The underlying skin in

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From the Department of Pediatrics, Ohio State University, and The Children's Hospital.

* Permission to report this case was granted by the patient's physician, Dr. Sophie Rogers.

Fig. 1.—Note the superficial acne and the fissuring of the lips. The hair is abundant, though loose. Later alopecia became moderately severe.

Fig. 2.—This photograph demonstrates the desquamation of the soles of both feet. Similar desquamation was also present on the palms.

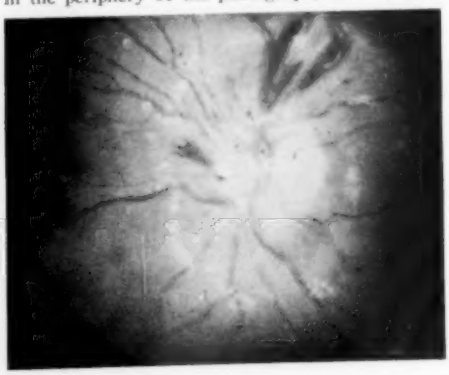
these areas was delicate and thin. Nikolsky's sign was absent. The scalp hair was dry and loose. There was moderate alopecia. Pubic and axillary hair was normal. Eyes: External examination was normal. There was bilateral papilledema (proved by binocular ophthalmoscopy), and linear hemorrhages surrounded each disc (Fig. 3). Abdomen: Liver and spleen were not enlarged. Extremities: The patient had tenderness in both legs, more on the left, particularly medial and inferior to the tibial tubercle. There was no swelling, heat, or redness. There was no weakness, sensory disturbance, or reflex changes, nor were there signs of meningeal irritation. Mentation was normal to bedside testing.

Laboratory Data.—Hemoglobin, 12.9 gm/100 ml.; white cell count, 8050 per cubic millimeter, with a normal differential count; platelets, normal on appearance. Serum chemistry studies: blood urea nitrogen, 24 mg/100 ml.; CO_2, 21 mEq/liter; chloride, 102 mEq/liter; total base, 149 mEq/liter; total protein, 7.3 gm/100 ml.; albumin, 3.6 gm/100 ml.; globulin, 3.7 gm/100 ml.; calcium, 10 mg/100 ml.; inorganic phosphate, 3.5 mg/100 ml.; alkaline phosphatase, 3.5 Bodansky units; cephalin flocculation, 1+; thymol turbidity, normal; cholesterol, 94 mg/100 ml.; protein-bound iodine, 9.6μg/100 ml. (Sept. 20); repeat, 4.8μg/100 ml. (Oct. 25). B. M. R., normal. Skeletal survey, including long bones, spine, and skull, was normal. Lumbar puncture (supine) yielded crystal-clear fluid, initial pressure 600 mm. H_2O; cells, 3 per cubic millimeter; sugar and protein, normal. EEG, normal. Fasting serum carotine and xanthophyll (Sept. 11), 264μg/100 ml. (normal, 75μg. to 150μg.) and 135μg/100 ml. (normal, 40μg. to 80μg.), respectively. On Feb. 4, 1957, these values were 195μg/100 ml. and 98μg/100 ml., respectively. The fasting vitamin A levels are shown in Figure 4.†

Course.—A diagnosis of chronic hypervitaminosis A was made on admission, and all medications were discontinued. Symptoms and signs began to abate within a week and the patient was entirely asymptomatic, except for continued loose hair, after two weeks. She was discharged on Sept. 17, 1956. When she was examined on Oct. 6, no abnormalities, except alopecia and superficial acne vulgaris (unchanged from before), were noted. Ophthalmoscopic examination was entirely normal, with no residua of the retinal hemorrhages. Regrowth of scalp hair, which was of fine texture, was not observed until six weeks after the vitamin A was stopped. Menstrual periods became normal

† Dr. Gilbert B. Forbes, Department of Pediatrics, University of Rochester School of Medicine and Dentistry, performed the serum vitamin A, carotene, and xanthophyll determinations.

Fig. 3.—Retinal photograph, showing papilledema, venous engorgement, and perivascular hemorrhages, particularly in the right upper quadrant. The oval spots, particularly noticeable in the periphery of the photograph, are artifacts.



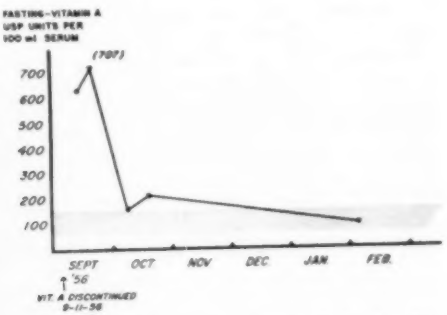


Fig. 4.—Fasting serum vitamin A levels. The shaded area indicates the normal range. Symptoms and signs had subsided by early October (see text), at which time the serum vitamin A level was still elevated.

in duration two months after medication was stopped. She has remained asymptomatic for nine months.

Comment

The first report of chronic hypervitaminosis A in humans was recorded by Josephs, in 1944, when he described the findings in a 3-year-old child.[1] Since then, a total of 27 reports among infants and toddlers has appeared in the English literature.[2-18] Six cases have been reported in adults.[19-24] In 1956, Pickup, in England, described the first two cases of hypervitaminosis A occurring in the British Isles.[25] Both were in children beyond the age group heretofore described, namely, 6 and 4 years of age, respectively. The present case is the third to be reported in children beyond 3 years of age. Thus, a total of 36 cases of chronic vitamin A intoxication have been recorded. They are summarized in the Table.

As is illustrated by the present case, the symptoms, signs, and laboratory findings can be ascribed chiefly to the involvement of three systems: the integumentary, the osseous, and the central nervous system. The incidence of these symptoms and signs and laboratory findings is shown in Figure 5. The commonest manifestation has been bone pain and tenderness, which has been observed in 34 of the 36 cases. In infants and toddlers the pain and tenderness has often been associated with subcutaneous swelling without redness or heat. Pain, tenderness, and swelling are most commonly observed over the long bones of the upper and lower extremities. Swelling of the feet due to involvement of the metatarsals is also frequently reported, with pain and tenderness sufficient to limit walking. The occiput has been the site of swelling in several instances. Accompanying x-ray changes have been observed in all infants and toddlers but in only one of the nine children and adults. In the latter instance this consisted of calcification of the infrapatellar ligament and the ligamenta flava. A bone biopsy in that case revealed calcification in the intercartilaginous tissues, with thickened periosteum.[22] The usual x-ray changes consist of cortical hyperostosis similar in all respects to the hyperostosis described in infants by Caffey. Less commonly, mottling or osteoporosis of the bone may be seen. Osteoporosis has not been conspicuous, although in the laboratory animal it is a prominent manifestation, leading to spontaneous fractures. Of interest, however, is the fact that two instances of craniotabes associated with hypervitaminosis A have been observed in the infant group.[13, 18] X-ray changes are most commonly seen in the ulnas, metatarsals, clavicles, and ribs. In none of the reported cases has the mandible been involved. This serves as an important differentiation from infantile cortical hyperostosis.

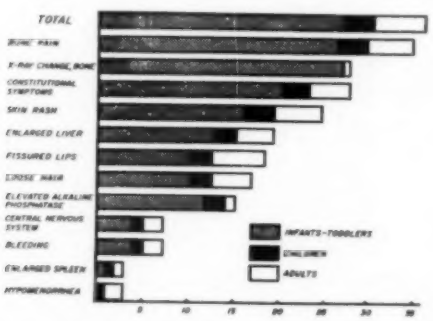


Fig. 5.—Incidence of symptoms, signs, and laboratory findings of chronic hypervitaminosis A in infants-toddlers, older children, and adults.

Constitutional symptoms, including anorexia, irritability, failure to gain weight, or actual loss of weight, have been the next commonest symptoms in this group of patients. These symptoms are believed to be related to the bone pain and tenderness and also to pruritis. Anemia has occurred in only a few cases and has been apparently of nutritional type, related most probably to poor appetite.

Involvement of the integument in this disorder consists of three disturbances: skin eruption, fissuring of the lips, and loose hair. The eruption, which frequently is intensely pruritic, most commonly consists of a maculopapular, occasionally slightly pigmented, eruption over the entire

Summary of Reported Cases of

Case No.	Sex	Vitamin A Dose, Units	Dose Duration, Mo.	Age at Onset of Therapy, Mo.	Age at Onset of Symptoms, Mo.	Age at Diagnosis, Mo.	Bone Pain	Constit. Symptoms	CNS Symptoms or Signs	Menstrual Disorder
Infants										
1	M	240,000+	33	3	26	36	+	+	0	..
2	M	250,000 (0–21 mo.) 500,000 (21–23 mo.)	23	Birth	21	23	+	+	0	..
3	F	250,000 (12 mo.) 400,000 (18 mo.)	30	6	18	36	+	0	0	..
4	M	125,000	13	1	5	14	+	+	0	..
5	F	50,000 (10–16 mo.) 100,000+ (16–22 mo.)	12	10	18	22	+	+	0	..
6	F	150,000	Several	—	19	25	+	+	0	..
7	F	200,000 300,000	9	12	19	21	+	+	0	..
8	M	400,000 600,000	6	6	11 ½	12	+	0	0	..
9	M	12,500 (0–17 mo.) 250,000 (17–32 mo.)	15	17	31	32	+	+	0	..
10	M	125,000 250,000	6	12	18	18 ½	+	±	0	..
11	M	100,000	7+	>17	22	24	+	±	0	..
12	M	200,000 300,000	17	20	32	37	+	0	0	..
13	F	37,500	17	12	28	29	+	+	+	..
14	M	120,000 (2 wk.-4 mo.) 480,000 (4–16 mo.)	15 ½	½	5	16	+	+	0	..
15	M	120,000 180,000	Many	?	22	24	+	+	0	..
16	F	400,000 500,000	24	12	35 ½	36	+	+	0	..
17	F	185,000	9	25	34	36	+	0	0	..
18	M	240,000	3+	>25	26	28	+	+	+	..
19	F	250,000	14	1	14	15	+	+	0	..
20	M	>100,000	18	12	28	30	+	+	0	..
21	F	240,000	13	4	10	17	+	+	+	..
22	F	30,000 80,000	6 ½	Birth	6	6 ½	+	+	+	..
23	F	480,000	8 ½	½	2	9	+	+	?	..
24	F	240,000	12	24	33	36	+	+	0	..
25	F	150,000 300,000	7	17	18	24	+	+	0	..
26	M	200,000 480,000	27	1	28	28	+	+	0	..
27	M	200,000	7	13	20	20	0	+	0	..
Older children										
1	M	200,000 463,040	5 ½ yr. 6 wk.	5 mo. ? 6 yr.	6 yr.	6 yr.	+	+	0	..
2	F	347,280	2 yr.	2 yr.	4 yr.	4 yr.	+	+	0	..
3	F	200,000	10	13 yr.	14 yr.	14 yr.	+	+	+	+
Adults										
1	F	600,000	18	42 ½ yr.	43 ½ yr.	44 yr.	+	+	0	+
2	M	200,000 275,000	2	25 yr.	25 yr.	25 yr.	+	+	0	..
3	F	150,000	4 yr.	48 yr.	49 yr.	52 yr.	+	+	0	+
4	F	500,000	8 ½ yr.	19 ½ yr.	21 yr.	28 yr.	+	+	+	?
5	M	50,000	3 yr.	51 yr.	52 yr.	54 yr.	0	+	+	..
6	F	160,000 180,000	7	21 yr.	21 yr.	21 yr.	+	0	0	..

* Normal, 60 to 160 U. S. P. or International units per 100 ml.
† Normal, 17 μg. to 45 μg. per 100 ml.
‡ Normal, 10 to 20 blue units per 100 ml.

Chronic Vitamin A Intoxication

Skin Lesions	Loose Hair	Fissured Lips	Bleeding	Vit. A Level/100 Ml.	Bone X-Ray Changes	Enlarged		Alk. Phosphatase, Bod. U.	Author
						Liver	Spleen		
0	+	0	+	910 U. S. P. units *	+	+	+	+ (18.7)	Josephs [1]
+	+	+	+	234 μg. †	+	+	0	?	Toomey & Morissette [3]
+	+	0	0	943 I. U. *	+	+	0	+ (17)	Dickey & Bradley [5]
+	+	+	0	2081 I. U.	+	+	0	+ (11.9)	Rothman & Leon [6]
+	+	+	?	660 I. U.	+	+	0	N (8)	Rothman & Leon [6]
0	0	+	0	--	+	0	--	+ (18)	Caffey [8]
0	0	+	0	330 I. U.	+	0	--	--	Caffey [8]
+	0	0	0	1384 I. U.	+	0	--	+ (15)	Caffey [8]
0	0	0	0	--	+	0	--	+ (19)	Caffey [8]
0	0	0	0	1395 I. U.	+	+	--	N (9.7)	Caffey [8]
0	0	0	0	--	+	0	0	--	Caffey [8]
+	0	0	0	--	+	+	--	+ (22)	Caffey [8]
+	+	--	--	--	+	--	--	+ (14.9)	Berry [9]
+	0	0	0	1630 I. U.	+	+	0	+ (35)	Fried & Grand [7]
+	0	0	±	2500 I. U.	+	+	0	+ (26)	Fried & Grand [7]
+	0	+	0	127 μg.	+	--	--	N (7.7)	Wyatt et al. [9]
0	0	0	0	--	+	--	--	--	Rineberg & Gross [9]
+	--	+	0	1040 I. U.	+	0	0	--	Bair [10]
+	0	0	0	259 I. U.	+	0	0	--	Cl. Case 623 [11]
+	+	+	0	837 μg.	+	+	--	N (12)	Gribetz et al. [12]
0	+	0	+	--	+	0	0	+ (16.3)	Gribetz et al. [12]
0	0	0	0	257 μg.	+	+	0	+ (17.9)	Arena et al. [13]
0	+	0	0	1121 I. U.	+	+	--	N (3.4)	Naz & Edwards [14]
+	+	+	+	2670 I. U.	+	0	0	N (3.8)	Reyerbach et al. [14]
+	0	0	0	100 blue U.‡	+	+	--	N (6.8)	Goldzier et al. [14]
+	0	+	0	"4+ elevated"	+	+	0	--	Harrison & Mercer [17]
0	±	0	? (Anemia)	472 μg.	+	0	0	N (3 K. A.)	Tudor [18]
+	+	+	0	450 I. U.	0	+	+	+ (25)	Pickup [15]
+	+	+	+	700 I. U.	0	+	—	+ (40)	Pickup [15]
+	+	+	0	707 I. U.	0	0	0	0 (3.5)	Oliver
+	+	+	0	--	0	0	0	0	Sulzberger & Lazar [16]
+	+	+	0	237 μg.	0	+	0	N (7)	Shaw & Niccoli [19]
+	+	+	+	--	0	0	0	--	Bifulco [21]
+	+	+	0	2000 μg.	+	+	+	N +	Gerber et al. [22]
0	0	0	4+ Guaiac	69 μg.	0	+	0	--	Bloch [23]
+	0	+	0	832 μg.	0	+	0	N (2.2 K. A.)	Elliott & Dryer [24]

body. Coarsening of the skin often precedes the eruption. Desquamation, particularly of the palms and soles, as noted in the present case, is commonly observed. Fissuring and scaling of the lips and looseness of the hair leading to alopecia have been observed in all of the older children, in the majority of adults, and in about one-third of the infants and toddlers. The eyebrows and the axillary and pubic hair may also be involved. Before looseness occurs, it is frequently noted that the hair becomes dry and coarse. Liver enlargement has occurred in approximately one-half of the cases. Liver-function tests, when performed, have been normal.

Central nervous system involvement has not been a common manifestation, but, as demonstrated in the present case, it constitutes an important sign. The signs and symptoms are the result of elevation of cerebral spinal fluid pressure. Abrupt rise in CSF pressure with attendant symptoms of headache, nausea, vomiting, and vertigo are the most prominent symptoms in acute intoxication with vitamin A. These symptoms have been described in adults since as early as 1597, when the symptoms were described by Gerritt de Veer[26] following the ingestion of polar bear liver. Other polar explorers subsequently have reported similar symptoms which have clearly been demonstrated to be due to the high concentration of vitamin A in the livers of many polar animals.[27] In children, as well as adults, acute vitamin A intoxication is characterized by central nervous system involvement. Marie and Sée[28] observed four children less than 12 months of age, three of whom ingested a single dose of 300,000 to 350,000 units of vitamin A or a vitamin A and D preparation. Toxicity emerged in the fourth infant after a similar total dose, but this was given over a six-day period in the form of nose drops. The authors demonstrated that the effects were due to vitamin A alone and not to the combination of A and D by giving 350,000 units of vitamin A to six additional infants, three of whom developed acute hydrocephalus. Symptoms and signs of increased spinal fluid pressure occurred within 24 hours and were manifested by projectile vomiting, tense and bulging fontanel, irritability, restlessness, insomnia, and drowsiness. Except for an increase in intracranial pressure there was no abnormality of the cerebral spinal fluid, and symptoms subsided within 48 hours. The most striking example of central nervous system involvement among the cases of chronic hypervitaminosis A is that of a 28-year-old woman reported by Gerber.[22] Seven years prior to diagnosis she developed headache, nausea, and diplopia and was noted to have nystagmus, strabismus, and papilledema. Spinal fluid pressure was increased. Ventriculograms were normal. A subtemporal decompression was performed, and the area remained bulging and tense for seven years, during which time the patient continued to ingest excessive amounts of vitamin A. Prior to the correct diagnosis, neurologic diagnoses included brain tumor, encephalitis, and chronic meningitis. The increased intracranial pressure promptly subsided when vitamin A was discontinued. Hydrocephalus has occurred in three children less than 3 years of age with chronic hypervitaminosis A. One child with typical skin and bone changes of hypervitaminosis A had increased spinal fluid pressure and a subdural hematoma.[6] Whether the latter was associated with hypervitaminosis A is not known. In experimental animals with hypervitaminosis A bleeding into the subcutaneous tissues, around spontaneous fractures, in the brain, and in the viscera is a common finding. The mechanism is believed to be antagonism between excessive vitamin A and vitamin K, with resultant hypoprothrombinemia. It is not clear whether vitamin A interferes with absorption of vitamin K or with its action within the liver. In humans, bleeding has not been a prominent manifestation. In addition to the child with subdural hematoma, one patient had rather severe bleeding of the gums following dental extraction, which subsided coincident with the administration of vitamin K,[21] and

another had a severe hemorrhage following tonsillectomy.[1] Unfortunately, coagulation studies were not performed in either patient. Indeed, in only one instance has an abnormal prothrombin time been observed, and this was not a constant finding in that case. Children with hypervitaminosis A have frequently demonstrated minor epistaxes, but whether this is related to vitamin A intoxication or to the rather common occurrence in this age group is not known.

In the present case and in two of three adults hypomenorrhea has been observed, and in all cases the menstrual periods have promptly returned to normal after cessation of the medication. No other endocrine disturbances are reported, although there have been hints suggesting inhibition of thyroid function by vitamin A. It was for this reason that protein-bound iodine and basal metabolic rate were obtained in the present case, with normal results. In experimental animals antagonism between excess vitamin A and thyroxin appears to be quite well established.[29]

Laboratory studies for the most part are within the normal limits. Calcium and phosphorus metabolism is not altered, and no case of hypercalcemia has been described. This helps to rule out the consideration of vitamin D intoxication occurring concomitantly with hypervitaminosis A. This combination has never been reported, probably because the dose of vitamin D in the usual A and D preparations, such as percomorph liver oil, is not large enough to cause intoxication with vitamin D. In 12 of 21 infants and toddlers in whom an alkaline phosphatase determination was obtained the level was elevated beyond normal (greater than 13 Bodansky units). In the two children described by Pickup there was striking elevation of the alkaline phosphatase, and in one adult, the patient with ligamentous calcification, the alkaline phosphatase was elevated on occasion.

The mechanisms whereby prolonged administration of vitamin A causes toxicity remain unknown. This subject has recently been excellently reviewed by Nieman and Klein Obbink.[29] In laboratory animals Wolbach has demonstrated that the skeletal changes are due to acceleration of the epiphyseal cartilage sequences, absorption of bone, and appositional bone growth. These changes are in conformity to normal bone pattern. Linear growth in animals is normal or may be impeded, but it is never accelerated. Fractures often occur in animals and can be explained by the extensive loss of previously formed cortical bone before the newly formed bone has acquired firmness sufficient enough to meet mechanical requirements.[30]

The cause of increased cerebral spinal fluid pressure is entirely mysterious. Most authors believe that the increase is due to excessive production of cerebral spinal fluid. However, there is little experimental evidence for this. Of interest, increased intracranial pressure has also been described in vitamin A deficiency, both in laboratory animals[31] and, more recently, in children.[32] Similarly, increased intracranial pressure has been described in hypophosphatasia[33] and following oxytetracycline, chlortetracycline, and tetracycline therapy.[34,35] Whether there is a common mechanism in these clinically unrelated conditions is not known.

The most important differential diagnosis in the infant and toddler age group is a consideration of infantile cortical hyperostosis (Caffey's disease).[36] Both hypervitaminosis A and Caffey's disease share as common manifestations bone pain, soft tissue swelling, irritability, and x-ray changes. In the past it has been emphasized that the differential diagnosis could be made on the basis of age—infantile cortical hyperostosis occurring before one year of age and hypervitaminosis A after one year. That this is not the case is demonstrated in Figure 6. In 6 of the 27 infants and toddlers the onset of symptoms was before 12 months of age; in 4 of the 6 the onset was before 6 months. The diagnosis was established in three of the six children before 1 year, but

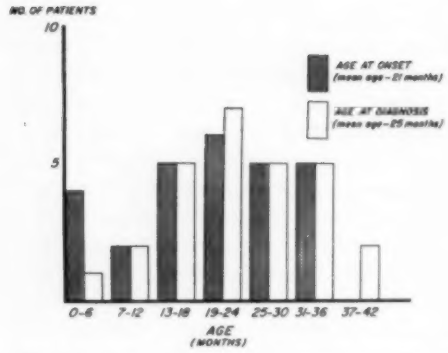


Fig. 6.—Age at onset and diagnosis of hypervitaminosis A in the infant-toddler age group. Note that six children (22%) had the onset before one year of age. There is little delay between onset and diagnosis in this age group (see also fig. 8).

in only one was it made before 6 months. While age does not serve in the differential diagnosis of these two diseases, there are other differences which separate the two. In Caffey's disease there is often fever, an elevated white blood cell count ,and a rapid erythrocyte sedimentation rate. The distribution of bone lesions is another important differential point. The mandible, which is commonly a site of involvement in infantile cortical hyperostosis, has never been involved in a reported case of hypervitaminosis A. Cutaneous manifestations, which are common in vitamin A poisoning, are not an accompaniment of Caffey's disease. Finally, the diagnosis of hypervitaminosis A is established by the high vitamin A level in the serum.

The interval between initiation of the toxic dose and the onset of symptoms is shown in Figure 7. In more than half of the infants the interval was between 1 and 12 months. In only 2 of the total of 36 cases did symptoms occur in less than one month after the initiation of the high dose. Of interest, but not of significance, because of the small numbers in each sample, the average interval in both infants and adults from the onset of the toxic dose to symptoms was 10 months. It is clear that there is a latent period between the onset of high-dose therapy and the emergence of toxic symptoms. Many factors may be responsible for this delay, including individual variations in absorption, utilization, and excretion. One factor that appears established is that the liver must become saturated with vitamin A before symptoms arise. The excessive accumulation of vitamin A in the liver is believed to be responsible for the hepatomegaly which has been observed in more than half of the reported cases.

Once the symptoms have arisen, the interval before the diagnosis is established varies in the different age groups (Fig. 8). In the infant and toddler groups the diagnosis was established in all except 1 child

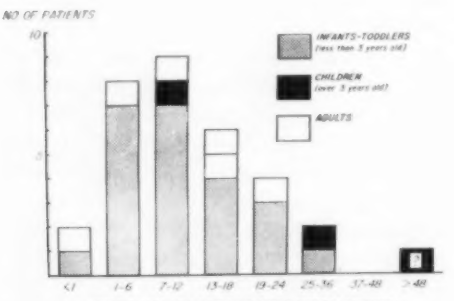


Fig. 7.—In all age groups there is a definite latent period between the initiation of excessive vitamin A intake and the emergence of symptoms of intoxication. The average interval is 10 months.

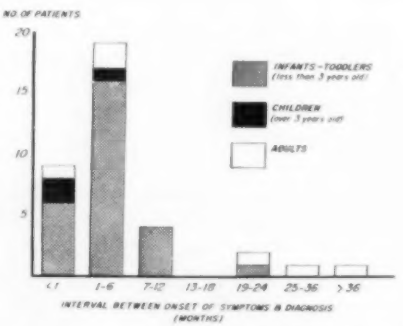


Fig. 8.—The interval between the onset of symptoms and diagnosis of hypervitaminosis A. In most infants (and all three older children) the diagnosis was made within six months of the onset of symptoms. In half of the adult group there was considerable delay before the diagnosis was considered.

by 12 months after the onset of symptoms and in 22 of the 27 within 6 months of the onset. In the three older children the diagnosis was established equally early, namely, within one month in two children and in my case two months after the onset of symptoms. However, in half of the six cases occurring in adults there was a considerable delay in the diagnosis, the longest being seven years. The reason for this appears to be that the manifestations of hypervitaminosis A, particularly the x-ray changes, permit rapid recognition in infancy, but in adults (and probably in older children, as more cases are described) without x-ray changes delay occurs until this diagnosis is entertained on other grounds.

The minimum toxic dose in man is not known. It has been estimated by Caffey that in children 1 to 3 years of age 100,000 units daily will result in chronic intoxication after a latent period of at least six months. There is no apparent relationship between age and dose, as can be seen in Figure 9. It can be seen that in four children and one adult toxicity occurred with the dosage of 100,000 units per day or less. The toxic dose in experimental animals has been reviewed by Nieman and Klein Obbink. There is considerable variation from species to species. Most of the work has been done in rats, and in this animal there is definite relationship of dose to age, younger animals being more susceptible. Few studies of chronic toxicity have been performed in humans. Josephs gave 500,000 units daily to an 8-month-old infant for four months without rise in fasting vitamin A level in the serum or emergence of symptoms. He also gave 200,000 units daily to two infants for "several weeks" without symptoms but with temporary rise in the serum vitamin A level lasting for one week. It is apparent from the paucity of cases, on the one hand, and the extensive use of vitamin A in large doses, on the other, there is great variation in the handling of vitamin A by individual persons, but most are able to excrete the medication rapidly enough to prevent accumulation. It also must be pointed out that none of the various carotinoids cause symptoms of hypervitaminosis A.[37] While large doses of β-carotene will result in yellow coloration of the skin (carotenemia) no other manifestations occur. The reasons for this appear to include the observations that carotene is less readily absorbed than vitamin A and that conversion into vitamin A is not rapid enough to allow accumulations of toxic quantities of vitamin A.

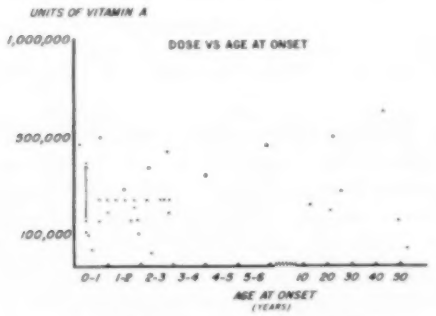


Fig. 9.—This figure demonstrates that there is no relationship between the dosage of vitamin A and the age of the patient. The frequency of dosage of 200,000 to 300,000 units in the infant-toddler age range is a reflection of the common usage of approximately 1 teaspoonful (4.9 ml.) of percomorph liver oil daily resulting in toxicity.

No therapeutic measures are indicated in chronic vitamin A intoxication. Withdrawal of the agent invariably results in prompt disappearance of symptoms. There are no prolonged sequelae of the disorder once the medicament is discontinued.

The recommended daily dose of vitamin A is 1500 I. U. in children up to 1 year, 2000 units from ages 2 to 3 years, 2500 units from 4 to 6 years, 3500 units from 7 to 9 years, and thereafter and in adults 5000 units per day except increasing to 6000 during pregnancy and 8000 units during lactation.[37-39]

In persons with biliary obstruction or steatorrhea vitamin A is poorly absorbed, because it is fat-soluble, and deficiency may ensue. Also, in cirrhosis of the liver vitamin A storage may be impaired. Therefore,

in these situations larger doses, up to 20,000 units daily, are indicated. Vitamin A administration in the recommended dosage will prevent the clinical manifestations of hypovitaminosis A, which include night blindness, xeropthalmia, and keratomalacia and, less importantly, skin changes, including follicular hyperkeratosis. As mentioned previously, increased intracranial pressure may also occur with hypovitaminosis A in infancy.

The indications for vitamin A administration in dermatologic diseases are not established. Some texts do not mention the use of vitamin A, while others suggest its use in conditions where there is excessive keratinization, either diffuse, as in icthyosis, or limited to the follicular system, as in acne vulgaris. For example, one text states "the dermatologic dose of vitamin A is 100,000 units per day, although in some disorders up to 300,000 units per day are required and treatment must be continued for a period of months to achieve the desired effect"![40] In general, dermatologic texts provide either very scanty or no information to the reader regarding vitamin A intoxication.[41-44] One commonly used textbook of medicine states that ". . . doses [of vitamin A] up to 300,000 units per day for a number of months have not produced detectable harmful effects. . . ."[45] The implication that such dosages are without risk is not consistent with the facts presented here. It is recognized that vitamin A in large doses is often prescribed by dermatologists. The extremely low incidence of chronic intoxication indicates that most persons can tolerate such doses. However, this does not justify its use, particularly when its value in skin disease is questionable. If prescribed for a "clinical trial," present evidence suggests that the dose should not exceed 50,000 units daily for a period of not more than two months.

Finally, in terms of better understanding the epidemiology of vitamin A intoxication, it is of interest to examine the reported cases for responsibility of prescribing the toxic dose. In 25 of the 27 cases among infants the family was responsible. In these situations the mother usually gave more than the prescribed dose because "it would do more good." In two of the infants the responsibility appeared to be with the physician, who in one instance prescribed high doses of vitamins for the diet and in the other, because of a large fontanel. Examination of the nine cases in older children and adults revealed that in seven of the nine cases the intoxication must be considered iatrogenic. In all of the older children vitamin A had been prescribed for skin conditions. This was also true in four of the six adults. In the present case some responsibility must also be placed with the patients, who did not discontinue therapy when this was recommended, although there was clear evidence of vitamin A intoxication before that time. In one adult advertising claims must be held as the responsible factor. Coupled with the claims of irresponsible firms are the facts that vitamin A in large amounts may be purchased without prescription over the druggists' counter or by mail, and, of even greater importance, I was unable to find indication on any label of vitamin A preparations that toxicity with large doses or prolonged administration might occur.

Summary

A case of chronic hypervitaminosis A in a 14-year-old girl is presented, and the English literature, comprising 36 cases in infants and toddlers, children, and adults, is reviewed.

The symptoms, signs, and laboratory findings are discussed. In general, all age groups share common symptoms and signs. X-ray changes of the long bones occurred in 100% of infants and toddlers but in only one of nine persons in the older groups. Central nervous system symptoms and signs due to increased intracranial pressure occurred in 20% of the total group.

All manifestations of hypervitaminosis A subside promptly following withdrawal of vitamin A. No sequelae were observed.

Age at onset does not serve as an absolute differential diagnostic point between hypervitaminosis A and infantile cortical hyperostosis. Six of twenty-seven infants and toddlers with hypervitaminosis A had the onset of symptoms before one year of age.

A latent period (averaging 10 months) between the initiation of excessive dosage of vitamin A and the emergence of symptoms is characteristic.

The normal daily requirement of vitamin A in all age groups is given. Except in situations of impaired fat absorption, the recommended daily dose should not be exceeded.

The value of vitamin A in large doses in certain skin diseases is questionable. A clinical dermatologic trial of vitamin A should not exceed 50,000 units daily for longer than one or two months. In 9 of the 36 cases of hypervitaminosis A an excessive dose of vitamin A had been prescribed by a physician.

Vitamin manufacturers should include a warning of possible intoxication due to excess dosage on the labels of vitamin A preparations. This is not the practice at the present time.

The retinal photograph was made by Drs. William Havener and Jack H. Prince, Department of Ophthalmology, The Ohio State University.

The Children's Hospital, 17th St. at Livingston Park (5).

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Gargoylism

A Review Including Two Occurrences in the American Negro

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Gargoylism was first reported by Hunter [1] in 1917, but it was not until two years later that the disease was described in greater detail by Hurler.[2] Clinically, the disease is characterized by skeletal dystrophy, coarse facial features, mental retardation, enlargement of the liver and spleen, and clouding of the corneas. When all of the stigmata are present, the disease is readily recognized. However, those cases lacking some of the characteristic criteria are classified as formes frustes.

The purpose of this paper is to present five cases, two of which were found in Negro children. The latter are believed to be the first documented examples of gargoylism in the American Negro. In addition, a review of the literature has been made, as well as a summary of the recent advances in the recognition and understanding of the fundamental defects of this disease process.

Report of Cases

CASE 1.—A 4-year-old Negro boy was admitted on Jan. 21, 1954, because of swelling of the legs and abdomen for one day. Two weeks prior to admission he had developed an upper respiratory infection. The patient was the product of what was thought to be a seven months' gestation, the birth weight being 2665 gm. (5 lb. 14 oz.). The family history was not contributory. He sat up with support at 7 months, walked at 18 months, and at 4 years could speak only a few words.

The physical examination on admission revealed a dwarfed 4½-year-old Negro boy. The temperature, pulse, and respiratory rates were normal. The head was markedly scaphocephalic, and the circumference was 58.8 cm. The eyes had marked clouding of the corneas, and the fundi could not be visualized. The bridge of the nose was extremely flattened, and a purulent discharge was present. The thoracic cage was increased in its anteroposterior diameter, and rachitic beading was observed in the ribs. Inspiratory rales were heard at the right base posteriorly. The heart was enlarged to percussion, and a rough Grade 2 apical systolic murmur was heard. The abdomen was moderately distended. The liver edge extended 6.0 cm. below the right costal margin, and the spleen was felt 2.0 cm. below the left costal margin. The hands were claw-like, with curvature of the fingers; the wrists and forearms were short and thickened. There was limited extension of the forearms. Pitting edema extended from the lower extremities to the presacral area.

Laboratory investigations revealed a hemoglobin level of 7.6 gm/100 ml.; the leukocyte and differential counts were normal. The total protein was 6.0 gm/100 ml.; albumin, 3.7 gm., and globulin, 2.3 gm/100 ml. The blood urea nitrogen was 25 mg/100 ml.

The examination of the skull revealed marked scaphocephaly and platybasia, with marked elongation of the sella turcica (Fig. 1). There was marked widening of the cardiac silhouette. An

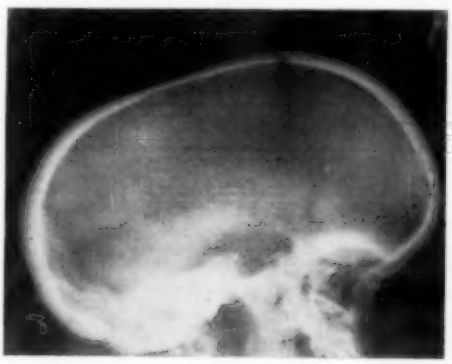

Fig. 1 (Case 1).—Lateral roentgenogram of the skull, showing scaphocephaly, platybasia, and elongation of the sella turcica.

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electrocardiogram was consistent with right auricular hypertrophy, with peaking of P waves in Leads II, aV_F and V_1. An electroencephalogram revealed a poorly organized pattern, with frequent biphasic spikes and sharp waves occurring throughout the tracing. Infrequent 14-per-second activity occurred with light sleep. No amplitude asymmetry or evidence of a focus was noted.

The patient was treated with digitalis, diuretics, and antibiotics. The edema abated, but the temperature continued to be elevated. The child died on the seventh hospital day.

Necropsy Summary.—At autopsy the following measurements were recorded: body weight, 13.7 kg.; crown-heel length, 97.9 cm.; pubis-heel length, 42.0 cm., and arm length, 29.0 cm. The head, which was markedly scaphocephalic, with prominent supraorbital ridges, had a circumference of 59.1 cm. (Fig. 2). The extremities and trunk

Fig. 2 (Case 1).—Negro child with coarse features, prominent supraorbital ridges, and scaphocephalic skull.

were short, and a dorsolumbar kyphosis was present. The hands were claw-like. The pericardial cavity contained 85 ml. of straw-colored fluid. The heart weighed 135 gm. (normal, 73 gm.). The epicardium and endocardium appeared to be slightly thicker than normal. The myocardium was firm and hypertrophied, the left and right ventricular walls averaging 1.1 cm. and 0.6 cm., respectively. A gray verrucal nodule measuring 0.2 cm. was noted on the auricular surface of the posterior cusp of the mitral valve. The walls of the coronary arteries were thickened. The liver weighed 960 gm. (normal, 516 gm.). Its surface was smooth and brownish-red, and on section the tissue was yellowish-tan.

The spleen was three times normal size, weighed 110.3 gm., was firm and reddish purple, and had prominence of the follicles. There was hypertrophy of the submucosal lymphoid tissue of the gastrointestinal tract. The sella turcica was

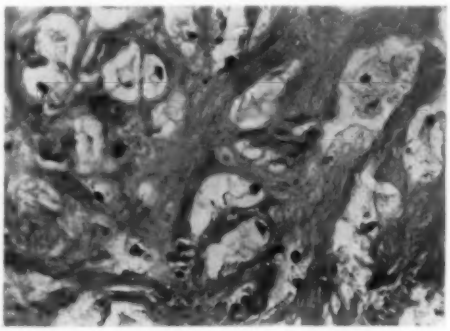
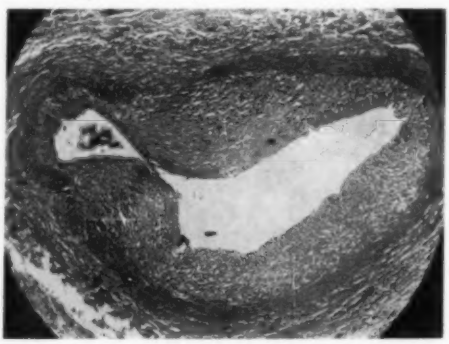


Fig. 3.—Myocardium with infiltration of large vacuolated cells and collagen. Hematoxylin and eosin; × 475.

markedly enlarged, but the pituitary gland was normal in size. The brain weighed 1490 gm. (normal, 1191 gm.) and was increased in its anteroposterior diameter. The meninges over the cerebral cortex were cloudy. Coronal section disclosed irregularity in the diameter of the cortex and subcortical white matter. There were areas of cavitation in the white matter of the occipital lobe. The lateral and third ventricles were twice the normal size.

Microscopic Examination.—The heart showed hypertrophy of the myocardial fibers, with focal swelling, loss of striations, pallor, and vacuolation. The most significant changes consisted of the proliferation of collagen and infiltration of large pale mononuclear cells (Fig. 3). The collagen was increased in the subepicardium and subendocardium, and strands of collagen from the latter penetrated the myocardium. These changes were more marked in the left side of the heart. There was also focal increase of collagen around the blood vessels. Pale oval cells infiltrated the areas of increased collagen. The cytoplasm appeared as a delicate reticular network and contained a few

Fig. 4.—Coronary artery with marked intimal thickening. Hematoxylin and eosin; × 20.



minute granules that stained pink with Masson's trichrome, periodic acid-Schiff, and eosin stains, but not with oil red O stain. The nuclei were oval and often eccentric and contained a single dark nucleolus. The first portion of the coronary arteries disclosed marked thickening and infolding of the endothelium due to proliferation of collagen and pale cells (Fig. 4), which were similar in appearance to those noted above. There was slight thickening of the media. The smaller branches of the coronary arteries revealed no change in the endothelium but showed marked thickening of the media. There was pallor, fenestration, and thinning of the elastic fibers of the media of the aorta. Oil red O stains were negative for free fat. Foci of emphysema and partial atelectasis were present in both lungs. All of the hepatic cells were filled with vacuoles which were positive for fat with use of oil red O stain. The majority of vacuoles were several times larger than the hepatic nuclei. Small numbers of lymphocytes infiltrated the edematous fibrous tissue of the portal triads. The vacuoles in the hepatic cells did not stain with alcian blue or with periodic acid-Schiff stain, and no change was noted following digestion with saliva. The spleen had no foam cells or increase in fibrous tissue, and the red pulp was moderately congested. The adrenals had vacuolation of the cells of all zones of the cortex. There was ballooning of many of the cells of the proximal convoluted and collecting tubules of the kidneys. The collagen around the interlobular arteries was increased and contained a few foam cells. There were foci of lymphoid hyperplasia of the follicles of the ileum and infiltration of lymphocytes, foam cells, and reticulum cells into the submucosa and mucosa. The lymph nodes were edematous and contained lipophages. Examination of the rare anterior horn cells of the cervical cord disclosed absence of Nissl substance. The ganglion cells of the gray matter were reduced in number. Several of the blood vessels in the white matter were surrounded by edematous brain tissue, giving a halo effect. No cellular infiltration was noted, and the vessel walls were not thickened. No fat was demonstrated by use of the oil red O stain. The meninges of the brain and cord were not remarkable. Sections of bone, which included a femur and all thoracic and lumbar vertebrae, were stained with hematoxylin and eosin. Although no vacuolated cells were seen, certain abnormal features were observed. The periosteum of the femur was irregularly thickened. The zones of proliferating cartilage of the vertebrae disclosed marked alteration. In many areas there was no evidence of recent growth. The cartilage cells on the diaphyseal side of the epiphyseal disk were not parallel to the long axis of the vertebrae. Instead, they were arranged horizontally and appeared to be in a resting state. The adjacent bony trabeculae rested on the cartilage in a horizontal plane. These inequalities of growth imparted abnormal shapes to the vertebrae and resulted in irregular compression of the vertebral spaces. Variations in thickening of cortical bone along the shaft of the femur were noted, together with irregularities in the degree of proliferating cartilage similar to that in the vertebrae. Normal hematopoietic units were contained in the marrow spaces. The remaining organs were not remarkable.

CASE 2.—A Negro girl was first admitted at the age of 2½ years because of a deformity of the back which had been noted at 4 months of age. The infant was born at term, weighing 3064 gm. (6 lb. 12 oz.). The family history was not contributory. She sat up alone at 7 months, but was unable to walk unassisted until 2 years of age. The speech was retarded, and at 2½ years she could utter only two or three words. She had had frequent respiratory infections since the age of 6 months.

On admission the patient was a poorly developed, deformed 2½-year-old child. The temperature, pulse, and respirations were normal. The expression was dull; the facies were coarse, with prominent supraorbital ridges. The head was large and scaphocephalic. The bridge of the nose was depressed, and the tongue protruded. The teeth were widely spaced, and a nasal mucoid discharge was present. A thoracolumbar kyphosis and slight scoliosis were noted. Examination of the eyes and fundi revealed no abnormalities. The heart and lungs were unremarkable. The liver and spleen were not palpable. The deep tendon reflexes were hypoactive.

A complete blood cell count and urinalysis were within normal limits. A Kahn test for syphilis was negative; glucose-tolerance test was normal; blood cholesterol, 123 mg/100 ml., and serum alkaline phosphatase, 12.6 King-Armstrong units. An x-ray examination revealed the cardiac shadow to be enlarged transversely. The ribs were broad and irregular in contour. The vertebral column had a scoliosis, kyphosis, and lordosis. The long bones of both lower extremities showed considerable widening and thickening of the diaphyses, with spreading at the epiphyseal ends. A Gesell test revealed this patient to have a developmental quotient of 30 (with a mental capacity of an imbecile).

The patient was discharged after three weeks and was readmitted five weeks later, on Oct. 19, 1944, because of a respiratory infection. Additional physical findings on this admission were genu valgum and flexion deformity of the hips and knees. A diagnosis of lipochrondrodystrophy was made by Dr. John Washington. The patient

continued to have repeated respiratory infections and was admitted in extremis and died on May 11, 1945. No autopsy was obtained.

CASE 3.—A 17-month-old white boy was admitted on Oct. 16, 1951, because of enlargement of the head since the age of 6 months. The infant was born at term, weighing 3260 gm. (7 lb. 3 oz.). The family history was not contributory. His development had been slow, and he sat alone at 10 months and walked at 14 months. There had been progressive enlargement of the head since the age of 6 months. Frequent respiratory infections had occurred since early infancy.

Physical examination revealed a fairly well developed and well nourished 17-month-old white boy. The temperature, pulse, and respirations were normal. The head circumference was 54.0 cm., and the chest circumference, 50.0 cm. The facial features appeared coarse, and the corneas were cloudy. There was a marked thoracolumbar kyphosis. The hands were short and thick, and no fingernail was present on the index finger of either hand. A mucoid nasal discharge was present. The examination of the heart revealed no enlargement or murmurs. There were coarse rhonchi and wheezing sounds throughout both lung fields. The liver was palpable 4.0 cm. and the spleen, 6.0 cm. below their respective costal margins. The deep tendon reflexes were hyperactive and equal bilaterally.

A complete blood cell count and urinalysis were normal. A skeletal survey demonstrated an elongated sella turcica, marked hypoplasia of the second lumbar vertebra, and a shortening of the radius and ulna, with sclerosis and cortical thickening. The metacarpal bones were broad at their distal ends and tapered proximally. The bones of both hands had marked osteoporosis. X-ray examination revealed marked dilation of the entire ventricular system.

A diagnosis of lipochondrodystrophy was made, and the infant was discharged on Nov. 3, 1951. The family moved from the city, and no follow-up could be obtained.

CASE 4.—A 3-year-old white boy was admitted on July 4, 1955, for investigation of mental and physical retardation. The infant was born at term, and the birth weight was 3487 (7 lb. 11 oz.). A bilateral talipes equinovarus was corrected by the application of casts. He was able to sit alone at 7 months, walked alone at 11 months, and could utter single words at 12 months. He had always appeared husky, and his head had been large and his features coarse since early infancy. Respiratory infections had been frequent, and a left inguinal hernia was repaired at 10 months of age. At 2½ years, because of dry hair and skin, coarse facies, large protruding tongue, and dullness of expression, hypothyroidism was considered, and thyroid extract was given for two months. At 2½ years an electroencephalogram revealed no abnormalities.

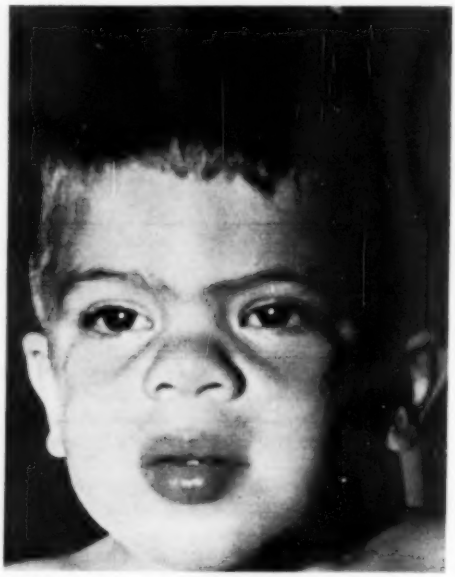
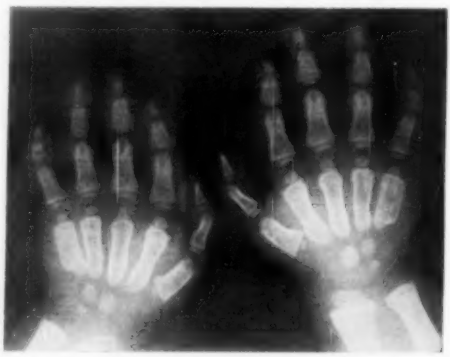


Fig. 5 (Case 4).—Typical facies of gargoylism.

Both parents were living and well. They denied knowledge of any condition in their families similar to that of the patient's. A possibility of consanguinity was suggested by the occurrence of identical surnames in the two families.

Physical findings on admission revealed a well-developed and well-nourished 3-year-old white boy. The temperature, pulse, and respirations were normal. The head was large, and the facies, coarse, with prominent supraorbital ridges (Fig. 5). The bridge of the nose was depressed, and

Fig. 6 (Case 4).—Roentgenogram of the hands, showing coarse trabeculation of the metacarpals with proximal tapering.



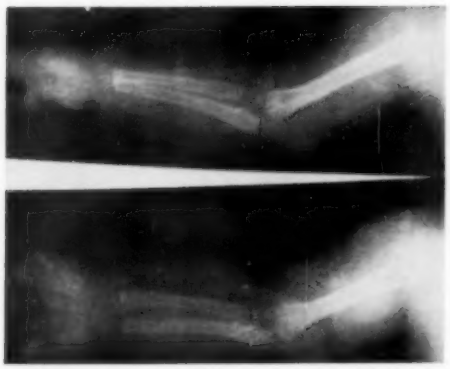


Fig. 7 (Case 5).—Roentgenogram of the upper extremities at 9 months of age, showing early osseous changes of Hurler's syndrome, consisting of irregularity of contour and thickening of the cortices of the radii and ulnae.

the tongue was large and protruded. The alveolar margins were hypertrophic. The fingers tapered and were short and thick, and the palms were broad. A pectus excavatum was present. A slight degree of thoracic kyphosis was noted.

A complete blood cell count and urinalysis were within normal limits. Blood smear showed basophilic granules in the polymorphonuclear leukocytes (Reilly bodies). A skeletal survey revealed considerable widening and thickening of the cortices of the long bones. The vertebral column had no abnormalities. The ribs were more widely spaced than normal. The sella turcica was elongated and shallow, and the cranium was large. The metacarpal bones were broad at their distal ends and tapered proximally (Fig. 6). The bones of both hands had osteoporosis. A diagnosis of lipochondrodystrophy (Hurler's syndrome) was made, and the child was discharged on July 6, 1955.

CASE 5.—A white boy, sibling of Case 4, was born at term by spontaneous delivery. The child appeared normal at birth except for syndactylism of the right hand. Because gargoylism was present in the sibling, roentgenographic studies were made during the first week of life, which revealed minimal epiphyseal cupping of the distal ends of the radii.

At 3 months of age the infant had normal growth and development, with no additional abnormalities. At 9 months he was seen at The Johns Hopkins University Hospital by Dr. Har-

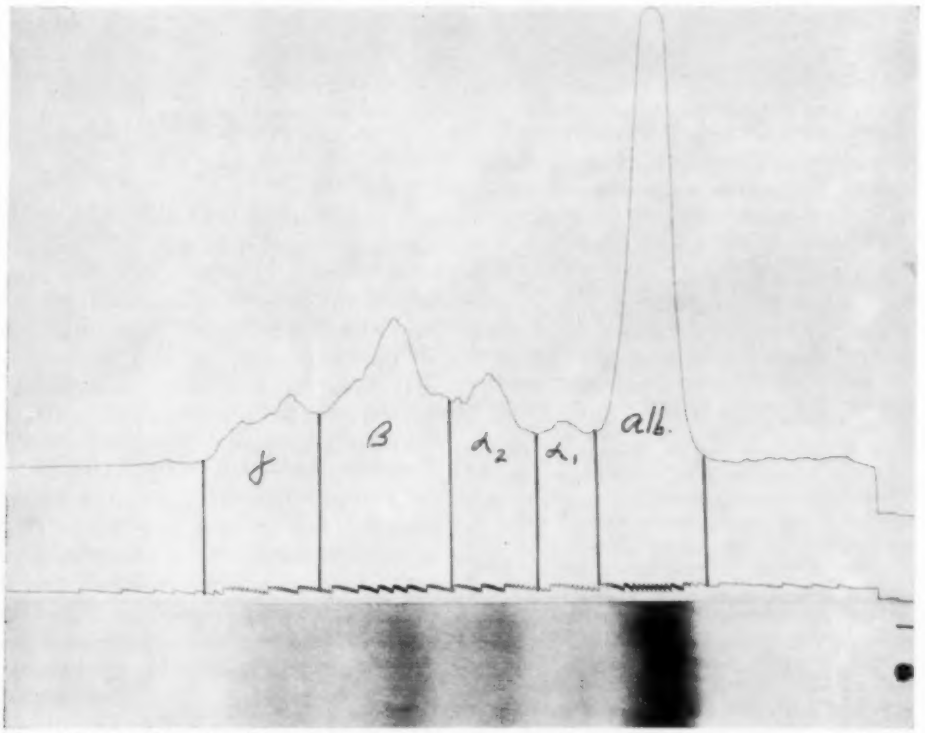


Fig. 8 (Case 4).—Paper electrophoretic serum protein pattern, showing a decrease in γ-globulin and in an increase in β-globulin.

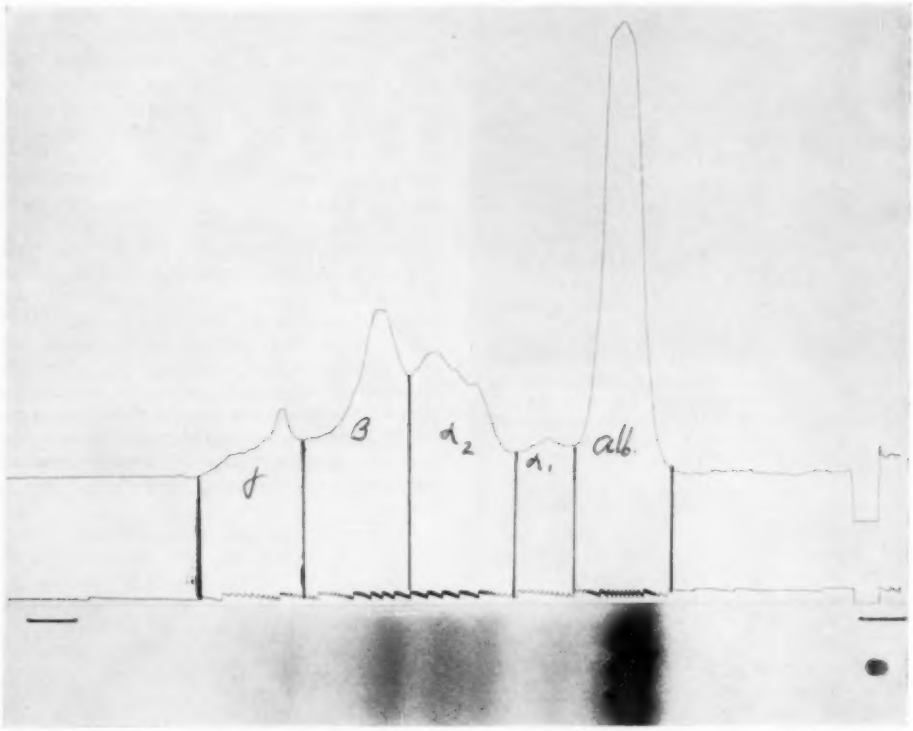


Fig. 9 (Case 5).—Paper electrophoretic serum protein pattern, showing an elevated α_2-globulin, the presence of a β-lipoprotein, and a decrease in γ-globulin.

riet Guild, who made a diagnosis of lipochondrodystrophy. At this time the infant showed definite physical retardation, a moderate degree of hypertelorism, and enlargement of the skull. There were prominent supraorbital ridges and frontal eminences. Roentgenological examination at this time showed enlargement of the cranium, with widening of the sutures, flattening of the bones of the skull, and a slight degree of elongation of the sella turcica. The bones of the upper extremities had an irregular contour, with thickening of the cortices (Fig. 7).

At 10 months of age the infant was admitted for repair of an incarcerated right inguinal hernia. The examination was essentially the same as at 9 months of age. Reilly bodies were identified in the leukocytes of the peripheral blood.

Serum Protein Electrophoresis.—An electrophoretic analysis of the serum protein pattern was made on the family of Cases 4 and 5. The serum protein concentrations of the parents were normal except for an increase in γ-globulin. The two children had a decrease in γ-globulin (Figs. 8 and 9). In addition, both patients had an elevation of β-globulin, while Case 5 had an elevation of α_2-globulin and a β-lipoprotein.

Comment

Approximately 200 cases of gargoylism have been reported to date, the majority being in the Caucasian race. Two cases have occurred in Chinese children.[3] Hubeny and Delano[4] have reported a case of "dysostosis multiplex" in a Negro child aged 7 years. This patient had marked shortness of the trunk, normal mentality, and no corneal opacities and was considered to conform more to the Morquio type than to the Hurler type of dysostosis multiplex. Ernould[5] has referred to a Negro child in Brazil, believed to be a case of gargoylism. However, no further information is available. Recently three cases have been reported from Khartoum in Sudanese natives.[6] Hurler's syndrome has a noteworthy familial occurrence. Cordes and Hogan[7] cited 11 instances in which two siblings were affected, and several families have had

three siblings with the disease. Cunningham [8] reported 12 male cases from a pedigree of a British family. Nja [9] has also reported sex-linked inheritance. There is only one recorded instance of Hurler's syndrome affecting the two children of different sex in a twin pregnancy.[10] Two forms of genetic inheritance are recognized. One is attributed to a sex-linked gene transmitted to males through their mothers, as in hemophilia.[9,11,12] The number of recorded examples of this type is small, but a common feature has been absence of corneal opacities. The other form is thought to be determined by an autosomal (non-sex-linked) recessive gene.[13] The predominance of males in reported cases is also seen in the present series. The majority of patients die before the third decade. However, Beebe and Formel [14] described nine cases in one family, five dying after the age of 40 and two still surviving at 43 and 45 years.

The clinical features of gargoylism are often not apparent until the end of the first year or even later. Thick skin and coarse features are characteristic of the syndrome. Washington [15] stated that although dwarfism is a marked feature later, height is not affected during the first four years of life. Limitation of extension of the joints is a fairly constant feature. Umbilical and inguinal hernias are often found. Mental retardation usually becomes apparent between the ages of 6 and 18 months. However, normal mentality has been observed in rare cases.[16-18] Hirsuitism of the trunk and extremities, as well as of the scalp, neck, and eyebrows is usually present. Vitiligo has been observed twice,[19,20] and specific cutaneous deposits have been described in one case of gargoylism.[21] The striking ocular finding is cloudiness of the cornea. It was observed only in Cases 1 and 3 of the present series. It usually appears between the first and third years of life. Convergent strabismus has been noted by some authors.[7,22,23] In several reported cases the corneas have been abnormally large.[17,24-28] Auditory acuity is often diminished early in the disease. Hypertrophy of the alveolar margins and irregular alignment and occlusion of the teeth are commonly seen. Deformity of the nasal and sphenoid bones causes a chronic nasal obstruction with frequent respiratory infections. Schwarz and Gagne [29] have reported a case of gargoylism in which liver involvement resulted in cirrhosis followed by hematemesis and death.

Formes frustes of Hurler's syndrome have been described by Jervis,[30] Strauss,[31] and de Lange and others.[32,33] These cases with incomplete and less striking clinical manifestations are often difficult to recognize. The problems involved in the differentiation of gargoylism from Morquio's disease are well summarized by Nöller [34] and Debré and others.[35] Böcker [36] has reported three examples of familial occurrence of both diseases. Some siblings suffered from gargoylism, while others were thought to have Morquio's disease. This would suggest that the two diseases are closely related genetically.

The laboratory findings in gargoylism include a mild hypochromic anemia and leukopenia with a relative lymphocytosis. Reilly [37] has described lilac-colored granules in the polymorphonuclear leukocytes, lymphocytes, and monocytes, which are seen with the Giemsa-Wright stain. The granules, which are presumed to be an abnormal storage substance, were identified in Cases 4 and 5.

The osseous changes in gargoylism are pathognomonic when fully developed. The bones of the skull, trunk, extremities, hands, and ribs may be involved. According to Caffey,[38] the basic lesion in tubular bones is swelling of the shaft with tapering of the ends of the bones. In contradistinction to the other osteochondrodystrophies, such as achondroplasia and Morquio's disease, the metaphyseal changes in gargoylism are minimal; the diaphyseal changes predominate. Osteoporotic and osteosclerotic lesions may occur. The osteoporotic type of

Hurler's syndrome bears roentgenological resemblance to Cooley's anemia. The configuration of the metacarpals is characteristic; they are broad at their distal ends and taper proximally. There is frequently some degree of hydrocephalus. A dilatation of the ventricular system was demonstrated by a pneumoencephalogram in Case 3, while the other four cases had definite enlargement of the skull. A shallow, elongated pituitary fossa is usually present and was seen in all of the present series in which skull x-rays were taken (four cases). Lumbar kyphosis and hypoplasia of the second lumbar vertebra are fairly constant features and when present are pathognomonic.[39] The scapulae are often high in position, are short and broad, and have irregular lateral borders.[40] An important contribution has recently been made by Caffey.[41,42] He reported neonatal roentgenological changes consisting of generalized rarefaction and metaphyseal spreading, cupping, and spurring in patients who later were recognized as typical gargoyles. These neonatal changes resemble those seen in rickets. The presence of these changes should aid in the early recognition of Hurler's syndrome in an infant in whose family there has been an occurrence of the disease. Case 5 showed, during the first week of life, early epiphyseal changes in the distal ends of the radii. This finding was helpful in prognosticating the later development of the overt manifestations of gargoylism.

Congestive cardiac failure appears to be the cause of death in well over 50% of the patients. Case 1 of this series died as a result of congestive failure and had gross cardiovascular damage at autopsy. A systolic murmur along the left border of the sternum was observed in 7 of 16 cases examined by Reilly and Lindsay.[43] These authors reported three cases with interventricular septal defects and one case with pulmonary stenosis in a group of eight autopsies.

Electroencephalographic reports in the literature are scanty. Abnormal tracings with no specific pattern or localization have been reported.[44-46] Case 1 had an abnormal pattern characterized by a dysrhythmia with frequent biphasic spikes and sharp waves. Cases 4 and 5 had no deviation from the normal. From the limited number of studies performed, there appears to be no characteristic electroencephalographic pattern in this disease.

The number of documented autopsies of patients with gargoylism is just under 40. However, not all are complete. The largest single series is that of Lindsay and others,[16] who recorded 8 in a group of 12 patients suffering from this disease. Although the autopsy findings are not constant, certain observations are commonly made. The hallmark of this disease is an abnormal storage of macromolecular substance in cells of the central nervous system, viscera, and supporting tissue, with proliferation of mononuclear cells, fibrous tissue, and collagen. Lindsay[47] emphasized the frequency of involvement of the cardiovascular system. He noted that 17 of 25 cases in which autopsy was done had cardiovascular damage. The necropsy of Case 1 presented by us revealed the cardiovascular system to be the major site of proliferation of mononuclear cells and collagen, which replaced the myocardium and scarred the mitral valve. Plaques may appear on the intima of the aorta, coronary, mesenteric, and other arteries, with resulting narrowing of the lumen. Kressler and Aegerter[48] recognized involvement of the liver, spleen, and lymphoid tissue as well as the cardiovascular system. In the present case no foam cells were found in the liver, the total enlargement being ascribed to the presence of neutral fat in the hepatic cells. Likewise, the spleen and lymph nodes were not involved. Lindsay and others[16] noted that neutral fat deposited in the hepatic cells did not account for the increase in the size of the cells. The enlargement, rather, was due to the presence of the abnormal storage substance. In contrast to the situation in other storage diseases, the reticuloendothelial system is

not affected regularly in gargoylism. However, according to Thannhauser and Schmidt,[49] the abnormal storage substance accumulates in the parenchymal tissues as well as in the reticuloendothelial system. The finding of deformity and dwarfism of the skeleton is not dependent on the presence of the abnormal storage substance or proliferation of foam cells and collagen. Case 1 of our series furnishes an example of this. The failure of bone and cartilage to develop normally results in a slow, irregular growth. The mechanism underlying the osseous changes is still obscure.

There are few reported accounts of the examination at autopsy of the eyes of patients who have had Hurler's syndrome. Kressler and Aegerter [48] described a wide separation of the laminae of the stroma in the cornea of an 8½-year-old child. Other authors [27,31,50,51] have described cells with faintly eosinophilic granular cytoplasm beneath the corneal epithelium. Wexler,[52] using Mallory's aniline blue-orange G stain, observed orange-red streaks between the lamellae of the cornea and sclera. The stromal cells were swollen with reddish-staining granules, which he presumed to be a glycogen. Bishton and others [53] examined the left eye of a child who died of gargoylism and found a calcified cataract and vascularized cornea. No abnormal cells were found in the cornea.

The pathological changes of the brain in gargoylism may simulate those of juvenile amaurotic idiocy and other storage diseases.[54] Dawson [55] observed that 10% of the neurones of the brain and cord in cases of gargoylism had vacuolation. It was concluded that the stored substance was a phosphatide or cerebroside. No abnormal storage substance was found in the brain or cord of the case autopsied in this series, but there was a decrease in the gray matter of the cortex.

Ashby and others [26] in 1937 analyzed the brain of a case of gargoylism for total lipid and cerebroside content. They found no excessive deposition of lipids in the cortex. De Lange and others [33] were the first to suggest that the substance accumulating in the cells in this disease might be a glycogen. Strauss [31] studied the tissues in one case of gargoylism by chemical analysis and found an increase in the lipid content of the liver and brain. This lipid was found to be simple fat, but many vacuolated cells in the heart, aorta, spleen, and ribs were negative for fat stains. In 1948 Lindsay and others [16] first used periodic acid-Schiff stains in frozen sections and obtained deep-red-staining material, which led them to think that the infiltrate was a complex carbohydrate. They also demonstrated small amounts of lipid substances. Jervis,[30] in 1950, also reported positive periodic acid-Schiff staining from two cases and a positive result with Feyrter's thionine stain, and he concluded that the infiltrate was probably lipoidal in nature. Brante,[56,57] after studying cases of gargoylism by histochemical analysis, found that the storage substances in the nerve cells were chiefly gangliosides, which were also found in the kidney tubules, splenic cells, and, to a much smaller degree, in the corneal and connective tissue cells. Besides this lipid storage, a nonlipid type of inclusion was present in almost all of the tissues affected except the nerve cells. This substance was found to be a mucopolysaccharide containing hexosamine. In a polysaccharide structure, hexosamine is a constituent of both gangliosides and mucopolysaccharides. Brante suggested that flooding of the tissues with mucopolysaccharides may be a consequence of some congenital enzyme disturbance. Histochemical studies were also reported by Dawson.[55] He concluded that the neuronal infiltrate was a relatively insoluble mucopolysaccharide-phosphatolipid compound and that the material outside the central nervous system was a freely diffusible mucopolysaccharide. Uzman [58] has recently isolated the storage substance from spleens and livers of patients who had gargoylism. He found that the stored material consisted of two components, a complex

polysaccharide and a water-soluble glycolipid. The conclusion was that "gargoylism represents a genetically induced defect in the metabolism of structural polysaccharides." Bishton and co-workers,[53] after studying the tissues of a case of Hurler's syndrome, found the glycogen in the liver to have been replaced by complex mucopolysaccharides. They also identified a heparin-like polysaccharide in the liver, but the substance was not found in the brain or spleen. The polysaccharide was positive with the toluidine blue stain but took the periodic acid-Schiff stain poorly or not at all. Although the nerve cells contained abnormal granules of a substance staining positively with periodic acid-Schiff reagent, the brain, on chemical analysis, showed no significant increase in the amounts of cerebrosides or gangliosides. Stacey and Barker[59] analyzed the liver from a patient with gargoylism and concluded that a reduction in the normal glycogen storage and an increase in a series of complex mucopolysaccharides had occurred. Mucopolysaccharides probably play an important role in the synthesis of supporting structures, which explains the growth deformities of the skeleton and related tissues.

Amino-aciduria has been reported recently in two children with Hurler's syndrome.[60] The amino acids identified in the urine were valine, tryptophan, leucine, phenylalanine, tyrosine, arginine, proline, and cystine.

Electrophoretic analyses of the serum proteins of patients with gargoylism have been studied by Löwenthal.[61] He found a fairly consistent increase in the α_2 fraction. This is not surprising, since polysaccharides are contained in this fraction.[62] In the two patients of the present series who had electrophoretic studies of the serum (Cases 4 and 5), a decrease was noted in the γ-globulin; an elevation, of the β-globulin, and only Case 5 had an elevated α_2 fraction, together with a β-lipoprotein.

Summary

Five patients with gargoylism are presented. Two Negro children are included. These two cases of gargoylism are believed to be the first reported in the American Negro. A presentation of the physical abnormalities, laboratory studies, and pathological examination in these patients is correlated with the cases recorded in the literature. Electrophoretic determinations of the serum from two cases were made. These studies revealed a decrease in γ-globulin, with an increase in β-globulin in one case. The electrophoretic pattern of the other patient was characterized by an elevation of the α_2-globulin, the presence of a β-lipoprotein, and a decrease in γ-globulin. It is believed that the increase in β-globulin, the decrease in γ-globulin concentration, and the presence of a β-lipoprotein represent new observations in this disease. The recent identification of the storage substances of gargoylism should provide a better understanding of this disease.

Drs. William F. Burdick and Dorothy V. Whipple gave permission to include their cases. Dr. John A. Washington gave advice in the preparation of the manuscript.

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Abstracts from Current Literature

A. M. A. Archives of Internal Medicine, Chicago

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Clinical Diagnosis of Sickle-C Disease.—Since the discovery that the hemoglobin molecule in sickle-cell anemia differs from normal adult hemoglobin, a number of other abnormal hemoglobins have been described. When the hemoglobin S, which is found in patients with sickle-cell anemia, and the abnormal hemoglobin C are present in the same person, a characteristic syndrome may occur, which is designated as sickle-C disease. Hemoglobin C is said to occur in 2% of the American Negro population. Until recently it was thought that the heterozygous combination of hemoglobins S and C was a benign inherited abnormality of the erythrocyte. Recently it has been found that these patients have an illness which does not follow the classic pattern of sickle-cell anemia. The present report points up the clinical difference between sickle-cell anemia and sickle-C disease and the authors report five of their own cases of proven sickle-C disease. It is felt that when a Negro patient with a positive sickle-cell preparation has the findings of (1) arthralgias, (2) abdominal cramps, (3) splenomegaly, and (4) more than 30% target cells in the peripheral blood that an accurate clinical diagnosis of sickle-C disease is possible. Arthralgia was the most consistent symptom, varying from a severe monarticular arthritis with a hot swollen joint to vague knee and elbow pains. Ulcerations are seen infrequently. Splenomegaly is present in 80% of the reported cases reported in the literature. This frequency of splenomegaly is in direct contrast to the small and often atrophic spleen of sickle-cell anemia.

Treatment of Mumps Orchitis with Adrenal Hormones.—The authors report on their experience with treating 23 patients with severe mumps orchitis by the use of cortisone, prednisone, or corticotropin. In all cases there was a rapid defervescence and reduction of testicular swelling and pain. There were no untoward effects of these hormones upon the course of the infection. The authors feel that these results obtained with the corticosteroids have been so striking that these hormones deserve wider trial in the treatment of orchitis. It is of interest to note that 9 of the 11 cases in which liver-function tests were performed showed definite abnormalities, which consisted of slight to moderate increase in the serum bilirubin, positive flocculation tests, and slight elevation of the serum alkaline phosphatase.

Isolated Pulmonary Cryptococcosis.—The authors report a case of isolated pulmonary cryptococcosis in a 15-year-old boy. This patient was successfully treated by means of a lobectomy, and the clinical, surgical, and pathological aspects of the disease are discussed. The vast majority of cases of human cryptococcosis have shown involvement of the central nervous system, with the lungs believed to be the next most frequently diseased site. The finding of isolated pulmonary cryptococcosis without evidence of involvement of the central nervous system is rare. The importance of prompt therapy of pulmonary cryptococcosis is

pointed out because it is felt that the Cryptococcus organisms may disseminate from lesions in the lung. The diagnosis in the case reported was made only after surgery.

The Identification and Clinical Significance of Casts.—Uroscopy is probably the most frequently indicated laboratory test and the one with the highest practical yield in the physician's office. However, this valuable test is too often delegated to the casually trained technician or to a commercial laboratory. It is felt that this test can and should remain in the physician's hands. The author outlines a detailed and simple method for the examination of casts, and the article contains numerous and clear photographs. The significance of various casts and combinations in the sediment is discussed, and clinical correlations are made between urine sediments and renal pathology. This article does not lend itself to abstraction but should be read in the original by every physician who treats patients with renal disease.

Acute Pulmonary Histoplasmosis.—The authors report two proved cases of acute pulmonary histoplasmosis with strong presumptive evidence of three other infections in one family in north central Pennsylvania. The occurrence of acute histoplasmosis outside of the previously known endemic areas is of interest and should make physicians everywhere alert to the possibilities of this disease. Both of the two proven cases were treated with cortisone after the first two weeks of illness, with good results. However, it is felt that steroids should not be used in the routine case of acute pulmonary histoplasmosis but should be reserved for those cases with continuing toxemia and severe prostration, and it should not be used until time has elapsed for adequate antibody formation.

American Journal of Pathology, Ann Arbor, Mich.

33, No. 3 (May-June) 1957

* Auto-Immune Hemolytic Anemia: II. Morphologic Observations and Clinicopathologic Correlations. Henry Rappaport and William H. Crosby.—p. 429.

Regeneration and Malformation in the Nervous System, Eye, and Mesenchyme of the Mammalian Embryo After Radiation Injury. Samuel P. Hicks, Barbara L. Brown, and Constance J. D'Amato.—p. 459.

Anatomical and Functional Studies of the Lung Deprived of Pulmonary Arteries and Veins, with an Application in the Therapy of Transposition of the Great Vessels. Romeo A. Vidone and Averill A. Liebow.—p. 539.

Auto-Immune Hemolytic Anemia. II. Morphologic Observations and Clinicopathologic Correlations.—In 36% of 50 cases of acquired hemolytic anemia of the autoimmune type there was congestion of the splenic cords in association with relatively empty sinuses. This feature, which is characteristic of congenital spherocytic anemia, was frequently associated with hyperplasia of the sinusoidal lining cells, another characteristic of congenital spherocytic anemia. The spleens, in contrast to those in congenital spherocytic anemia, contained a large amount of hemosiderin pigment and erythrophagocytosis was frequent. The presence of spherocytosis and increased osmotic fragility could be correlated with congestion of the splenic cords in the cases of acquired hemolytic anemia. These observations were held to support the concept that a selective retention of morphologically abnormal erythrocytes contributes to the patient's anemia. However, neither spherocytosis nor congestion of the cords seemed to have any bearing on the patient's response to splenectomy.

Annals of Internal Medicine, Lancaster, Pa.

45:331-560 (Sept.) 1956

The Present Status of Etiologic Discovery in Viral Diseases. John F. Enders.—p. 331.

* The Importance of the Fractional Serum Bilirubin Determination in Clinical Medicine. C. J. Watson.—p 351.

Pseudomembranous Enterocolitis and Antibiotics. C. R. Newman.—p. 409.

Constrictive Pericarditis: A Review and Long-Term Follow-Up of 78 Cases. John C. Dalton, R. J. Pearson Jr., and Paul D. White.—p. 445.

Infiltrative Eosinophilia. R. S. Díaz-Rivera, F. Ramos-Morales, M. R. García-Palmieri, Z. R. Sotomayor, and A. A. Cintrón-Rivera.—p. 459.

Varicella Pneumonia. Ray G. Cowley, William E. Crew, and Gerard R. Hassett.—p. 518.

Congenital Aneurysm of the Noncoronary Sinus of Valsalva Leading to Complete Heart Block. Edmon B. Lee, Oscar J. Krieger, and Norman K. Lee.—p. 525.

45:561-736 (Oct.) 1956

Fructosuria. Alfred R. Lenzner.—p. 702.
The Rh-Hr Types: A Complex Problem in Serology, Genetics, and Nomenclature. A. S. Wiener and I. B. Wexler.—p. 725.

The Importance of the Fractional Serum Bilirubin Determination in Clinical Medicine.—Van den Bergh, who first applied the diazo reaction for the determination of bilirubin, recognized that it proceeded in two phases, a prompt direct reaction, requiring seconds, and an indirect reaction, beginning in two to four minutes and greatly accelerated by the addition of alcohol. Subsequent studies of time reaction curves have shown that the main period of transition occurs at about one minute; therefore, measurement of the direct value should be made at this time. Direct-reacting bilirubin is water-soluble, or polar, while indirect-reacting bilirubin is chloroform-soluble, or nonpolar. Recently, it has been shown that indirect-reacting bilirubin is indistinguishable from chemically pure, free crystalline bilirubin. The older concept that indirect-reacting bilirubin is a complex with the protein globin now seems unlikely. On the other hand, direct-reacting bilirubin has been shown to be a complex of bilirubin and an anion, probably glucuronic acid.

On the basis of an analysis of 889 serum bilirubin determinations in 702 patients with one-minute values greater than 0.29 per 100 cc. or total bilirubin greater than 1.5 mg. per 100 cc., the fractional determination has been useful in three respects. First, elevation of the one-minute fraction with normal indirect fraction occurs in preicteric or anicteric hepatitis, common duct stone without jaundice, hepatic carcinomatosis, and cases of cirrhosis with cholangiolitic features. In all of these situations the one-minute bilirubin is abnormal where the total bilirubin determination fails to reveal the presence of disease. Second, elevation of the indirect fraction with little or no increase in the direct fraction occurs in retention jaundice, which is due to hemolysis or impaired hepatocellular function. Certain cases of cardiac jaundice, some patients with subsiding infectious hepatitis, and the Gilbert type of constitutional hepatic dysfunction belong in this category. Third, in regurgitation jaundice both fractions are usually increased. Often this determination fails to distinguish between parenchymal and extrahepatic causes, but when the total bilirubin is elevated (>1.5) and the one-minute value is less than 40% of the total, extrahepatic obstruction may be considered very unlikely. Most cases of hepatitis and biliary tract cancer have ratios greater than 50%. Low ratios occuring in hepatitis or cirrhosis suggest the presence of hemolytic complications.

Circulation, New York

15, No. 3 (March) 1957

Isolated Congenital Mitral Stenosis: Report of Two Cases with Mitral Valvotomy in One. J. L. Braudo, S. N. Javett, D. I. Adler, and I. Kessel.—p.358.
Congenital Absence of the Pulmonary Valve. Lucien A. Campeau, Paul E. Ruble, and Warren B. Cooksey.—p. 397.

15, No. 4 (April) 1957

Bacterial Endocarditis Following Cardiac Surgery. Clarence Denton, Elias G. Pappas, Joseph F. Uricchio, Harry Goldberg, and William Likoff.—p. 525.
Interatrial-Pressure Relationships After Closure of Atrial Septal Defects in Man. Albert H. Pemberton, John W. Kirklin, and Earl H. Wood.—p. 568.
American Heart Association: Congenital Cardiac Defects; A Physician's Guide for Evaluation and Management. Ruth Whittemore, S. Gilbert Blount Jr., Sidney Blumenthal, Frank Gleen, Edward C. Lambert, and Helen B. Taussig.—p. 631.

Isolated Congenital Mitral Stenosis: Report of Two Cases with Mitral Valvotomy in One.—The authors report two cases of isolated congenital mitral stenosis in two young infants. The diagnosis in one was proved at autopsy. The other was diagnosed clinically; this patient is still living and moderately well 16 months after mitral valvotomy. The essential features of all the cases of isolated congenital mitral stenosis previously reported in the literature supplemented with their two cases are studied. The authors described symptoms as usually beginning at birth, but with possible delay until 2 years of age. Growth failure and dyspnea were common in most cases. The most frequent physical findings were congestive failure, cardiomegaly, apical systolic murmur, and accentuated pulmonic second sound. Periodic episodes of cyanosis did occur but were not persistent.

Chest plates revealed cardiac enlargement, pulmonary plethora, and left and usually right atrial enlargement together with right ventricular hypertrophy. Angiocardiography was diagnostic, since the dilated left atrium retained the dye for an abnormally long time because of the stenosed mitral valve. The pathologic changes in the mitral valve were described.

The Journal of Pediatrics, St. Louis

50, No. 6 (June) 1957

Aminophylline Toxicity. H. Soifer.—p. 657.
Massive Spasms. D. H. Chao, F. M. Taylor, and R. Druckman.—p. 670.
A Study of Acute Respiratory Disease in Infancy. W. C. Taylor and C. H. Read.—p. 679.
Congenital Defects in Infants Following Mumps During Pregnancy. J. Holowach, D. L. Thurston, and B. Becker.—p. 689.
* Pneumoencephalography in Tuberculous Meningitis. J. E. Sifontes, S. V. R. Sordillo, and E. M. Lincoln.—p. 695.
Congenital Afibrinogenemia. B. J. Grossman and R. E. Carter.—p. 708.
Enterobiasis in Children. M. E. Jenkins.—p. 714.
Pretibial Fever Due to Leptospira Pomona. J. G. Stroup and H. D. Riley.—p. 716.
Cutaneous Moniliasis in Infants. R. C. V. Robinson.—p. 721.
Dysplasia Epiphysialis Multiplex. W. Levy, H. Mazumdar, and F. Morales.—p. 724.
Congenital Unilateral Multicystic Kidney Associated with Maternal Rubella. E. L. Lipton and L. J. Scordamaglia.—p. 730.
Duodenal Compression by the Mesenteric Artery. M. Prouty and W. L. Waskow.—p. 734.
Clinical Pathological Conference, Children's Medical Center, Boston, Mass.—p. 738.
Suicide in Children and Adolescents. H. Bakwin.—p. 749.

51, No. 1 (July) 1957

The Normal Pulmonary Arterial Pressure During the First Year of Life. R. D. Rowe and L. S. James.—p. 1.
The Pattern of Response of Pulmonary and Systemic Arterial Pressures in Newborn and Older Infants to Short Periods of Hypoxia. L. S. James and R. D. Rowe.—p. 5.
The Ductus Arteriosus in the Neonatal Period. S. C. Mitchell.—p. 12.
* Clinical and Pathological Observations in Infants With Coarctation of the Aorta and Patent Ductus Arteriosus. D. Goldring, W. A. Thomas, E. McCoy, R. M. O'Neal, and M. R. Behrer.—p. 18.
Nitrogen Metabolism of Infants Fed Human and Cow's Milk. L. A. Barness, D. Baker, P. Guilbert, F. E. Torres, and P. Gyorgy.—p. 29.
Effect of Lactose on Nitrogen Metabolism and Phenol Excretion in Infants. D. A. Cornely, L. A. Barness, and P. Gyorgy.—p. 40.
Serum Akerfeldt Test for Schizophrenia in Children. B. S. Brown.—p. 46.
The Management of Hypertrophic Pyloric Stenosis in a Community Hospital. F. P. Ross and W. Pick.—p. 49.
BCG Vaccination in Virginia. E. L. Kendig Jr.—p. 54.
Infantile Amaurotic Family Idiocy. P. J. Kozinn, H. Wiener, and P. Cohen.—p. 58.
Treatment of Acute Purulent Meningitis with Tetracycline. R. Koch and H. Hansen.—p. 65.
Brain Abscess in Infants. R. A. Munslow, V. S. Stovall, R. D. Price, and C. M. Kohler.—p. 74.
Infarction of the Testicle in the Newborn Infant. P. S. Pinto and J. N. Kiefer.—p. 80.
Changes in the Heart and Lungs at Birth. L. S. James.—p. 95.
Intrauterine Fetal Oxygenation. R. J. Blattner.—p. 115.

Pneumoencephalography in Tuberculous Meningitis.—The authors point out that tuberculous meningitis is now a curable disease but it is important to try and diagnose it and prevent neurological sequelae. They also state that neurological sequelae may result from cerebral thrombosis with consequent necrosis. It may also result from disturbed cerebrospinal fluid circulation, most commonly at the base of the brain, resulting in a communicating form of hydrocephalus. This hydrocephalus may give signs or symptoms or may not. It may occur during the acute phase or develop insidiously while the patient appears to be improving. In Dr. Lincoln's autopsy series it was shown that the occurrence of hydrocephalus bore a direct relation to the severity and duration of the disease. The authors referred to other reports on pneumoencephalography in tuberculous meningitis.

The authors performed pneumoencephalography on three groups of patients with tuberculous meningitis: (1) those recovered or recovering, (2) a group studied early in the course of the disease and, (3) a small group during the later phase of treatment. A total of 38 air studies on 27 patients was performed. The patients tolerated the procedure well. The commonest reaction observed was fever of three or four days' duration.

The authors found hydrocephalus early in the course of the disease as well as late in the course. Of 10 patients with hydrocephalus, 5 died (one following an attempt at a shunt

and one five days after a pneumoencephalogram), 4 had sequelae of varying severity, and one was in good condition (41 to 60 months' follow-up). Of 15 patients with normal pneumoencephalogram, none died, and 4 had no sequelae, 5 were deaf, and the rest had deafness with other sequelae. Two patients had no ventricular filling. Both recovered but were deaf, and one was epileptic.

The authors feel that a pneumoencephalogram should be done on a patient with tuberculous meningitis when the progress, chemical or clinical, is unsatisfactory. They feel, firstly, that it is a helpful prognostic sign and, secondly, that it will help determine modifications of therapy such as surgery.

Clinical and Pathological Observations in Infants with Coarctation of the Aorta and Patent Ductus Arteriosus.—The authors review 14 patients with coarctation of the aorta who had been autopsied in the department of pathology of Washington University. All the patients had been observed by at least one of the authors before death. Age of the patients was from 8 days to 8 months. The coarctation in all was just proximal to the attachment of the ductus arteriosus, and each had one or more defects permitting shunting of blood between systemic and pulmonary circulation. The authors reviewed blood pressure findings, ECG findings, x-rays, clinical notes, autopsy records, and microsections of the lungs.

Twelve of the fourteen infants had a blood pressure difference between upper and lower extremities of 20 mm. Hg or more. Four had a difference of 10 mm. Hg higher in right upper extremity over the left, and two had no difference between upper and lower extremities. Readings were done by the flush technique. Nine of the thirteen who had ECG's showed right ventricular hypertrophy and myocardial disease (inverted T waves). Two showed left ventricular hypertrophy. X-rays of 11 revealed that all had a marked degree of cardiac enlargement and 9 had pulmonary vascular enlargement. Symptoms started early, the commonest, in order of frequency, being poor feeding, dyspnea, tachypnea, and edema. The lumens of the aortas were severely constricted in the coarcted segments. A horizontal ridge was demonstrated on the intimal surface of the coarcted segment at the attachment of the ductus. There was a patent ductus in 11 of 14, interventricular septal defects in 9, interatrial defects in 4, and a truncus arteriosus in 1. Fibroelastic thickening of the ventricular endocardium was present in three.

The microscopical appearance of the pulmonary arteries varied. In two there was a complete loss of arteriolar muscle. In five the muscular walls of the pulmonary arteries were as thick as the newborn infant's. Charges similar to arteriosclerosis were found in three.

The authors discuss the possibilities of making an early diagnosis. Onset of symptoms was early. Physical findings, such as ashen-gray color, rapid and labored respirations, edema, enlarged heart with rapid rate, and a basilar systolic murmur, are usually seen. Liver and spleen are enlarged. ECG was not very helpful. X-ray findings of pulmonary vascular engorgement are helpful. Blood pressure findings of a greater than 20 mm. Hg difference between arms and legs are very helpful. The femoral pulse should always be palpated. If blood pressure is 10 mm. Hg or more higher in right arm than in left, then think of a coarctation with a long coarcted segment. Cyanosis of the lower half of the body was not seen in this series. In one case there was a slight but definite difference in arterial saturation between upper and lower extremities (blood sample from right upper extremity and while patient was breathing room air; when breathing O_2 the shunt in the ductus may be reversed).

The authors discuss treatment of these complicated cases. The usual medical regimen is advocated. Surgery has been successful in some, but the mortality rate is high. It is felt, however, that those patients with coarctation who develop failure early in infancy respond very poorly to medical management and, therefore, the only hope is surgery. The authors also feel that the presence of associated cardiac defects probably accounts for the early cardiac decompensation. They also feel that the child with coarctation who has no signs of cardiac failure should be watched and the operation should be performed at the usual time (8 to 10 years), but that those who go into failure early should probably be operated on as early as possible.

Maandschrift voor kindergeneeskunde, Leyden, Netherlands

25:1-32 (Jan.) 1957

* Vaccination Against Smallpox in Very Young Infants. H. J. Doorschodt.—p. 1.
* The Lipidogram in Lipoid Nephrosis. C. Hooft, C. Vandenberghen, and M. van Belle.—p. 19.

25:37-71 (Feb.) 1957

* Results of Bacteriological Analysis of Human Milk and Its Consequences for Pediatric Practice. D. A. A. Mossel and H. A. Weijers.—p. 37.
* Intestinal Duplication in Infants. J. J. Govers.—p. 64.

25:73-103 (March) 1957

The Treatment of Acute Rheumatic Fever. H. A. W. M. Tiddens.—p. 73.
* Hepatomyelia. R. Maertens.—p. 87.
A Case of Congenital Anemia with Multiple Congenital Deviations (Fanconi Syndrome). M. J. Delbeke.—p. 95.

25:112-138 (April) 1957

* Thrombopathy. S. van Creveld, Liem Khe Ho, and H. A. Veder.—p. 112.
Agenesis of a Branch of the Pulmonary Artery. M. G. P. Overwater.—p. 127.
* Investigations on Metabolism of Phenylalanine and Tyrosine in Vitamin C Deficiency in Children. J. H. P. Jonxis and T. H. J. Huisman.—p. 130.

Vaccination Against Smallpox in Very Young Infants.—The danger of postvaccinal encephalitis in the Netherlands is small when the children are vaccinated below the age of 2 years. Therefore vaccination usually is done between the ages of 6 and 12 months. However, many parents object to vaccination at this age because the children sometimes are very ill for some days after the vaccination. The authors investigated the advantages of vaccination against smallpox at a very early age, i. e., during the first 3 months after birth. During the investigation of more than 1000 infants whose ages varied from 6 weeks to 1 year he found that this vaccination was as successful as with older children. The quantity of antibodies (antihemagglutinins and virus-neutralizing antibodies) in the young infants on the average was only slightly smaller than in the older children.

The Lipidogram in Lipoid Nephrosis.—The lipidogram of 13 children with the nephrotic syndrome was studied by means of the method of Swahn (1953). Two kinds of curves were found. The first showed a fall in the α_1-lipoproteins, a sharp rise in the β-lipoproteins and a lowered or normal chylomicron fraction. The second type was found in most cases of lipoid nephrosis and had a rise in β-lipoproteins and chylomicrons and a fall in the α-lipoproteins: The first type was found in chronic nephrosis, in cases treated with corticotropin, and in nephrotic nephritis. The second type was found in two cases which had received several courses of corticotropin.

Results of Bacteriological Analysis of Human Milk and Its Consequences for Pediatric Practice.—A bacteriological analysis was made of 60 unselected samples of raw human milk obtained from healthy mothers and revealed total counts up to 2.3×10^8 per milliliter and colititers up to 0.6×10^8 per milliliter. In samples obtained with all practicable aseptic precautions, immediately cooled and stored at about 5 C, and analyzed within six hours, total counts up to 1.9×10^6 per milliliter, colititers up to 0.5×10^3 per milliliter, Streptococcus faecalis up to 0.6×10^4 per milliliter, and numbers of Staphylococcus aureus up to 0.2×10^6 per milliliter were found, originating from the microflora of the breast.

The authors are of opinion that only human milk with counts below 10^6 per milliliters may be used, but they must be pasteurized before use. Raw human milk may only be given to infants after a complete bacteriological analysis. Lyophilized human milk tends to oxidative rancidification and therefore must be packed with special precautions.

Intestinal Duplication in Infants.—Description of two cases. One presented as an acute ileus; in the other a tumor was found accidentally. A survey of the literature on the embryology and surgery of the condition is given.

Hepatomyelia.—Two cases of hepatomyelia induced by birth injury are described, and a description is given of the different clinical forms, the pathogenesis, and the symptomatology of this condition.

Thrombopathy.—The authors studied different functions of the platelets in 35 patients with thrombopathy and in some patients recovering from thrombocytopenia. In patients with thrombopathy a disturbance of the thromboplastic function could only occasionally be demonstrated by means of the thromboplastin generation test. According to the combination

of disturbances found in the examined functions of the platelets, the cases of thrombopathy were separated into a number of groups. However, a stricter classification will only be possible when more functions of the platelets can be accepted and the methods of examination of these functions have become more refined.

The conduct of the platelet functions in patients recovering from thrombocytopenia appeared to be greatly varying. Complete recovery of these functions usually took a much longer time than the normalization of the platelet count. In one case where this complete restoration of the platelet functions failed to occur thrombocytopenia developed again.

Investigations on Metabolism of Phenylalanine and Tyrosine in Vitamin C Deficiency in Children.—In three scorbutic children the oral administration of DL-phenylalanine and L-tyrosine caused a much higher excretion of tyrosine in the urine than in a control child, whereas the increase of the plasma levels of these amino acids was lower.

From these findings it is concluded that the amino-aciduria is of renal origin. Also, without additional tyrosine, the excretion of tyrosine by scorbutic children was found to be much higher than in normal children.

Medical Journal of Australia, Sydney

1, No. 2 (Jan. 12) 1957

* Cardiac Murmurs in School Children. Douglas Stuckey, Bryan Dowd, and Helen Walsh.—p. 36.
Innocent Systolic Murmurs of Aortic Origin. Douglas Stuckey.—p. 38.

1, No. 3 (Jan. 19) 1957

The Effect of Food on the Absorption of Penicillin Given by Mouth. E. R. H. Clarke, A. G. Mathews, Nancy D. Hesketh, and M. G. Evered.—p. 61.
A Study of Stillbirths in the State of Victoria—1953. F. M. C. Forster.—p. 72.

1, No. 4 (Jan. 26) 1957

A Child Guidance Case and Its Dynamics. Rose Rothfield.—p. 108.

1, No. 8 (Feb. 23) 1957

* Congenital Malformations and Maternal Rubella. David B. Pitt.—p. 233.

1, No. 9 (March 2) 1957

Kwashiorkor in New Guinea. P. S. Venkatachalam and V. Ivinskis.—p. 275.

1, No. 10 (March 9) 1957

Psychosomatic Disorders in Children. Felix Arden.—p. 312.
The Management of Breast Feeding and of Some Childhood Maladies in General Practice. Stuart Patterson.—p. 314.
Jaundice in Childhood. Felix Arden.—p. 316.

1, No. 12 (March 23) 1957

Kala-Azar in a Child of Five years. Andrew Rigg.—p. 389.

1, No. 13 (March 30) 1957

The Mortality of Childhood in Australia: II. The School Ages. H. O. Lancaster.—p. 415.

Cardiac Murmurs in School Children.—This study was a result of an investigation of 34,863 students in the Sydney metropolitan area. The ages ranged from 5 to 16 years. The total number of children reported to have a cardiac murmur was 467 (1.34%), and of these 364 attended clinics for further investigation. At these clinics physical examination was carried out by at least two observers "with special cardiological experience." Electrocardiograms and radiologic examinations were done in a large number, including all of those in which the presence of an organic lesion was suspected. A diagnosis of rheumatic fever was based upon the criteria of Jones (1944). Diagnosis of congenital heart was based on the criteria of Wood (1950). It is of interest that more than half of the children with congenital

heart disease had been previously investigated. Innocent murmurs were described as being midsystolic, short in duration, low in intensity, and usually maximal in the left parasternal line and there were no other laboratory or clinical findings. It is of interest to note that percentage distribution of the types of heart murmurs was nearly identical in all three of the heart centers carrying on this special investigation. The totals among those with heart murmurs are as follows: rheumatic heart disease, 10.3%; congenital heart disease, 20.7%; innocent murmurs, 69.0%. For comparison, these figures are similar to surveys in America, Canada, and England in relation to the total incidence of heart disease, but this study reveals a higher proportion of congenital heart disease. The authors state that previous surveys have revealed that between 40% and 58% of organic heart disease in school children is due to congenital abnormalities, whereas this survey in 1955 shows the incidence of congenital heart disease to be 66%.

Congenital Malformations and Maternal Rubella.—The author reviews much of the previous literature on the relationship of rubella to congenital malformations. He points out the discrepancy between the early studies from Australia and those from the United States, in which the former shows a much higher incidence of congenital malformations associated with maternal rubella in the first four months of gestation. He critizes the early studies in four major respects. Many relied upon the history of the mother to establish the diagnosis of rubella. At best, the diagnosis of rubella in the mother is difficult, and Pitt states that the perfection of rubella antibody tests will be extremely valuable in any future evaluation. One of the major criticisms is that a retrospective study, where abnormal cases are first collected and then the study works back to the history of the causal event, has many errors by its very nature. Finally, there is a good deal of "looseness" in the diagnosis of congenital defects. The present author reports on a series of 20 cases in which maternal rubella was accurately reported and the women were all followed in the same hospital. This study was compiled in the last eight years. In this series, 10 normal children were born, 2 of the 20 could not be traced, 3 were definitely abnormal, 1 was doubtfully abnormal, and the remainder were reported normal by the parents but did not receive an examination. The author concludes that the large incidence of congenital malformations initially reported from Australia was due to faulty statistical interpretations and that the risk is not nearly as great as was originally believed.

New England Journal of Medicine, Boston

256, No. 23 (June 6) 1957

Serum Enzymes in Muscular Dystrophy and Certain Other Muscular and Neuromuscular Diseases: I. Serum Glutamic Oxalacetic Transaminase. C. M. Pearson.—p. 1069.

Successful Treatment by Nephrectomy of Hypertension Resulting from Aorticorenal Embolus. P. W. Stone, J. B. McNally, J. W. Lord Jr., and J. W. Hinton.—p. 1076.

* Application of Homeostatic Principles to the Management of Nephrotic Patients. N. B. Talbot, J. D. Crawford, and C. D. Cook.—p. 1080.

Differential Serum Vitamin B_{12} Concentrations in Mothers and Infants. W. P. Boger, G. M. Bayne, L. D. Wright, and G. D. Beck.—p. 1085.

Medical Advice to Travelers. B. H. Kean.—p. 1088.

Gastrointestinal Polyposis with Mucocutaneous Pigmentation (Peutz-Jeghers Syndrome). T. L. Dormandy.—p. 1093.

Goiter of the Newborn: Report of an Unusual Case. C. S. Petty and R. L. DiBenedetto.—p. 1103.

256, No. 24 (June 13) 1957

Salmonellosis in Massachusetts: A Sixteen-Year Experience. R. A. MacCready, J. P. Reardon, and I. Saphra.—p. 1121.

* Clinical Manifestations of Salmonellosis in Man: An Evaluation of 7779 Human Infections Identified at the New York Salmonella Center. I. Saphra and J. W. Winter.—p. 1128.

Renal-Vein Thrombosis in Newborn Infants of Diabetic Mothers: Report of Two Cases. M. E. Avery, E. H. Oppenheimer, and H. H. Gordon.—p. 1134.

Gastrointestinal Polyposis with Mucocutaneous Pigmentation (Peutz-Jeghers Syndrome). T. L. Dormandy.—p. 1141.

Current Concepts in Therapy.—p. 1149.

256, No. 25 (June 20) 1957

Congenital Absence of the Corpus Callosum: Report of a Case and Review of the Literature. U. T. Slager, A. B. Kelly, and J. A. Wagner.—p. 1171.

Serum Amylase Levels in Experimental Intestinal Obstruction. J. J. Byrne and T. F. Boyd.—p. 1176.
* Transfusion Reactions in the Absence of Demonstrable Incompatibility. H. Fudenberg and F. H. Allen Jr.—p. 1180.
Acidosis in Renal Disease. W. B. Schwartz and A. S. Relman.—p. 1184.
Gastrointestinal Polyposis with Mucocutaneous Pigmentation (Peutz-Jeghers Syndrome). T. L. Dormandy.—p. 1186.
Nephropathy Associated with the Oral Administration of Zoxazolamine (Flexin): Report of a Case. T. Cohen.—p. 1193.

256, No. 26 (June 27) 1957

* Effect of Acetazolamide on Citrate Excretion and Formation of Renal Calculi: Report of a Case and Study of Five Normal Subjects. E. E. Gordon and S. G. Sheps.—p. 1215.
Ulcers of the Leg in Cooley's Anemia. F. Pascher and R. Keen.—p. 1220.
Studies in Intravascular Coagulation: V. A Distinction between the Anticoagulant and Antithrombotic Effects of Dicoumarol. S. Wessler, J. D. Ballon, and J. H. Katz.—p. 1223.
Caries Research in Laboratory Animals. R. F. Sognnaes.—p. 1226.
A New Rapid Clinical Test for Proteinuria. J. R. Leonards.—p. 1230.
Brief Recording: Aplastic Anemia After Meprobamate (2-Methyl-2-N-Propyl-1,3-Propanediol Dicarbamate) Therapy. L. M. Meyer, W. L. Heeve, and R. W. Bertscher.—p. 1232.

257, No. 1 (July 4) 1957

* Evaluation of Adrenocortical Function with Intramuscular Injection of ACTH Gel. V. DeFilippis and I. I. Young.—p. 1.
Use of Methyl Scopolamine Nitrate in the Treatment of Paroxysmal Fussing (Colic) in Infancy. M. A. Wessel.—p. 14.
Human Experimentation: Medicolegal Aspects. I. Ladimer.—p. 18.
Current Considerations of Esophageal Physiology, Normal and Abnormal. E. W. Wilkins Jr.—p. 24.

Application of Homeostatic Principles to the Management of Nephrotic Patients.—The authors point out the fact that, on the one hand, patients who have lost most of their normal capacity to eliminate water, potassium, and phosphate because of severe renal damage may satisfactorily take and eliminate large amounts of sodium and chloride, whereas, in contrast, patients with childhood nephrosis may fail to eliminate water and sodium in spite of normal renal function as judged by the conventional tests. They present evidence to suggest that this is facultatively determined and not necessarily the result of an intrinsic loss of renal capacity to excrete sodium salts and water.

Clearance data were presented of several children with various sodium and water loads imposed and also treatment with steroids and albumin. Patients on low and increased sodium diets were found to be able to excrete the sodium. At other periods some of these same patients were unable to excrete the sodium and water loads. One of the balance studies showed the beneficial effect of intravenously administered salt-poor albumin.

The authors present a working hypothesis of the edema in nephrosis and correlate the therapeutic procedures used with this hypothesis and with their balance studies. The basic lesion is thought to be fibrinoid degeneration of the basement membrane due to an antigen-antibody reaction. This leads to albuminuria, which leads to hypoalbuminemia, which leads to hypovolemia, which leads to renal sodium conservation and increase in body solute stores and also to renal water conservation. This, then, results in increased extracellular volume. The steroids tend to suppress the antigen-antibody reaction, thus reducing the albuminuria. Elimination of edema may also be induced by restoration of vascular osmotic pressure by albumin given intravenously. This will only be transient unless albuminuria is supressed. Gross limitation of sodium intake may block formation of edema at level of renal sodium conservation. However, homeostatic mechanisms are demanding sodium, and it is practically impossible to create a significantly negative sodium balance by this method. In edematous patients whose vascular volume is normal, nothing is gained by reducing sodium below ordinary levels. Diuretics such as mercury have been used in an attempt to lose sodium via the kidneys, but renal damage may be caused by this method. Furthermore, disturbing homeostasis may result in hypovolemia. Restriction of water intake only results in a fall of body (serum) water concentration and makes the patients very thirsty. Water loading does not seem to result in a sodium diuresis in nephrosis as it does in other diseases. Caution in removing edema fluid by paracentesis is urged because of the possibility of causing circulatory collapse. The edema fluid is thought to support vascular volume in conditions of hypoalbuminemia. If collapse occurs, treat with albumin, plasma, or whole blood.

Clinical Manifestations of Salmonellosis in Man: An Evaluation of 7779 Human Infections Identified at the New York Salmonella Center.—The authors present data on 9284 clinical and subclinical human Salmonella infections from 1939 to 1955. There were 86.5% isolated from stools, 8.3% from blood, 1.9% from pus, 0.8% from spinal fluid, and 2.6% miscellaneous. The grouping was as follows: A, 0.5%; B, 42.2%; C^1, 28.8%; C^2, 13.4%; D (excluding S. typhosa), 7.1%; E, 6.2%; F, G, H, I, other, 1.9%.

Four main types of disease produced were (1) gastroenteritis (68.3%), (2) typhoidal or septic syndrome (8.3%), (3) focal manifestations (7.4%), and (4) carrier state (15.5%). There were 4.1% deaths.

Gastroenteritis varied from a mild form to a severe form with rapid dehydration, convulsions, and death, or to a dysentery-like form. Bloody diarrhea was frequent in young children. Infants and the aged were sicker and had a higher mortality rate. All the salmonellas produced this. S. typhimurium was the commonest. In several cases, signs of generalized infection with high fever or focal manifestations or both developed some days or weeks after complete recovery from gastroenteritis. S. choleraesuis and S. paratyphi B were most apt to do this.

Typhoidal or septic syndrome was manifested usually by spiking temperature (sometimes continued), often with splenomegaly and occasionally a rash. Usually pulse rate was high and WBC count was elevated, with a shift to the left. Constipation was frequent. S. choleraesuis most commonly produced the septic type of the disease, whereas S. paratyphi A and B and S. panama often produced the typhoidal state.

Focal manifestations included appendicitis, cholecystitis, salpingitis, and peritonitis (146 cases), abscess (136 cases), pneumonia and pleurisy (85 cases), and bacterial endocarditis and pericarditis (20 cases). Most patients with meningitis were infants. Of 20 cases of subacute bacterial endocarditis, 13 were due to S. choleraesuis and 4 to S. typhimurium. S. choleraesuis was responsible for 35.7% of the cases of focal manifestations. S. bredeney produced 82 total infections of all kinds, of which one-fifth were focal, especially meningitis.

About one-half of the carriers had had a history of clinical infection. S. choleraesuis had a carrier prevalence of only 1.1%, whereas that of S. tennessee was 36% and those of S. anatum and S. newington were 25.4%.

The ordinary T. A. B. vaccine produces immunity to S. paratyphi A (which is rare here) and to the Salmonellas of Groups B and D. Group C, which had an incidence of 42% and has a higher morbidity and mortality rate (includes S. choleraesuis), is not affected by the vaccine.

Transfusion Reactions in the Absence of Demonstrable Incompatibility.—The authors report on transfusion reactions which occur even when they have been shown to be compatible by all known laboratory tests. Two cases were reported. In both cases retesting of original materials showed that the bloods were compatible. However, serum drawn several days after the reaction showed an antibody. The authors postulated three possible explanations: 1. No significant antibody was present but an anamnestic response occurred. 2. Abundant antibody was present in the spleen and other tissues but not in the circulating blood. 3. Antibody was present but not in quantities detectable by present methods. To try and find the reason studies of red cell survival were done in five persons.

The five persons were patients in whom specific isoantibodies had been previously demonstrated; in three circulating antibody was no longer detectable, while in two it was present in minimal amounts. Each subject was given 10 ml. of Cr^{51}-labeled red cells containing the antigen corresponding to the antibody previously demonstrated. Samples, drawn at various intervals, were tested for radioactivity measurement on whole blood and plasma, hematocrit value, plasma hemoglobin concentration, and titer of isoantibody if any detectable.

The results were as follows: Survival time of the transfused red cells was much shortened even though antibodies were not demonstrable previously (times of 55 minutes, 75 minutes, 8 hours, 9 hours, 12 days); there was a definite marked increase in radioactivity over the spleen as compared to the heart (very little in the liver); increases in plasma hemoglobin were definite and rapid, although not large. In the one case, where survival time was 12 days, there was a delayed rise of plasma hemoglobin to 16 mg/100 ml. at three hours but no detectable radioactivity increase over the spleen.

These studies did not answer the theories postulated but were useful from the practical point of view, because they showed that in spite of all tests a previously sensitized person may have a hemolytic transfusion reaction. The sensitization may have occurred through pregnancy.

The authors suggest the following procedures to try to avoid reactions: Use high protein media, proper incubation, and the indirect Coombs test; if weak agglutination is found, check the recipient's cells against his own serum; if there is still a positive weak agglutination, keep on searching for a donor; if compatibility cannot be decided by tests, give an adult patient no more than 50 ml. of blood and obtain a blood sample 10 or 15 minutes later; determine the plasma hemoglobin level of it and if this is over 10 mg/100 ml., then the blood is incompatible.

The authors also suggest that patients who need frequent transfusions (cases of hemophilia, etc.) be completely typed (A-B-O, Rh, M-N-S, Kell, Duffy, Kidd). They also suggest that their tests indicate that perhaps the reason for gradually increasing transfusion requirements (such as in Cooley's anemia) is subclinical sensitization. As an added precaution, they suggest that, in cases of elective surgery, the patient donate his own blood a few days before the operation, a procedure which guarantees compatibility.

Effect of Acetazolamide on Citrate Excretion and Formation of Renal Calculi: Report of a Case and Study of Five Normal Subjects.—The authors refer to the suggestion of Ostberg that citric acid in urine functions to keep relatively insoluble calcium salts in solution. Also, Harrison and Harrison demonstrated that in rats that had been fed acetazolamide the urinary citrate excretion was greatly reduced and precipitation of calcium salts in the urinary tract was striking.

The authors report the case of an 18-year-old boy who had been taking acetazolamide (Diamox) for three years and who presented with renal colic. X-ray revealed stones. All studies were negative. The patient and five normal controls were fed acetazolamide and urinary citrate, and calcium excretion and blood calcium level and citrate levels were followed. The results showed that on acetazolamide all test subjects showed a marked reduction in the excretion of citrate and of citrate-binding capacity of calcium in the urine. There was no change in calcium excretion nor in blood levels of calcium and citrate.

The authors believe that the calcium citrate is a soluble complex and is relatively undissociable. If enough citrate is not excreted, then calcium is free to form other salts. The authors refer to five other cases in the literature.

Evaluation of Adrenocortical Function with Intramuscular Injections of ACTH Gel.—The authors point out the value of exogenous corticotropin (ACTH) as a test of adrenal cortical function and the superiority of the determination of 17-hydroxycorticosteroids in the urine over the peripheral-blood eosinophil count. They review the testing material from crude corticotropin given intramuscularly to intravenously administered corticotropin and back to intramuscularly administered high-potency repository corticotropin (ACTH Gel). The intramuscular test with the latter has given different results in different hands. The authors review the test.

The test, as performed by the authors, consisted in measuring the excretion of 17-hydroxycorticosteroids (by a modified method) in the urine for a 24-hour period (if previously taking cortisone, patients stop taking it at least 24 hours previously). Then a dose of 100 units of repository corticotropin is administered intramuscularly and another 24-hour urine collection is tested for 17-hydroxycorticosteroid excretion.

Control subjects (adults) showed a mean rise of 19.0 mg. with a range of 5.5 to 39.4 mg. In Addison's disease there was no appreciable rise, even if corticotropin was administered for three days in a row. Five subjects on long-term corticoid therapy were studied (one was getting as little as 15 mg. cortisone daily for seven months). None of the five showed a normal rise after one day, but they did show a normal rise after two or three days or if the dose of repository corticotropin was 200 units. Three patients with Cushing's syndrome (due to bilateral adrenal hyperplasia) were tested. It appeared that in two a hyperresponsiveness was demonstrated after one test dose. When the repository corticotropin was given two or three days in a row it appeared to demonstrate a hyperresponsiveness in all. Two subjects on long-term corticotropin therapy also had normal responses.

Of five cases with myxedema, three responded normally, one did not respond, and the fifth did not respond with intramuscular administration but did with intravenous administration. Five normal subjects failed to respond, and it was found that response was normal with another lot, and it was, therefore, concluded that the material was substandard. One patient was discovered who was truly refractory to intramuscularly administered corticotropin but

responded to intravenous administration of corticotropin. Two factors in the test must be taken into consideration—one is extravascular inactivation of corticotropin, and the other is inadequate or variable absorption. The authors feel that this is seldom seen.

The authors conclude that the six- to eight-hour eosinopenic response to 100 units of repository corticotropin is a reliable screening test. They feel that the urine 17-hydroxycorticosteroid determination of the repository corticotropin is a definitive procedure in evaluating adrenal hypofunction. Occasionally (at present in persons on long-term corticotropin therapy or those with myxedema) it may be necessary to check with the intravenous test.

Pediatrics, Springfield, Ill.

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The Innocent (Functional) Cardiac Murmur in Children. D. H. Fogel.—p. 793.
Neurologic Manifestations of Leukemia: Report of Three Cases in Children Simulating Acute Bacterial Meningitis. E. F. Gilbert and E. C. Rice.—p. 801.
Skin Turgor as a Quantitative Index of Dehydration in Rats. Z. Laron and J. D. Crawford.—p. 810.
Skin Turgor as a Quantitative Index of Dehydration in Children. Z. Laron.—p. 816.
* The Maintenance Need for Water in Parenteral Fluid Therapy. M. A. Holliday and W. E. Segar.—p. 823.
The Brazilian Experience in Prevention of Tuberculosis with a Concurrent Method of BCG Vaccination. M. Olinto.—p. 833.
Concentration of Pyruvic Acid in the Blood of the Newborn Infant: Demonstration of Differences in Concentration between Maternal and Cord Circulation. R. F. Gonzales and L. I. Gardner.—p. 844.
Association of Transposition of the Great Vessels and Rudimentary Right Ventricle, With and Without Tricuspid Atresia. A. Kessler and P. Adams.—p. 851.
Granular Cell Myoblastoma in Childhood: Report of an Unusual Case. H. C. Bishop and B. M. Wagner.—p. 858.
Acute Jejunal Obstruction Secondary to Traumatic Intramural Hematoma. F. E. Moody.—p. 863.
Isolation of Type I Poliomyelitis Virus from Human Cerebrospinal Fluid. M. G. McCrea.—p. 869.
Facial Paralysis in Poliomyelitis: A Follow-Up of 58 Patients. S. T. Winter.—p. 876.
Studies of the Pharynx: I. Poliomyelitic Disabilities of the Upper Pharynx. J. F. Bosma.—p. 881.
Hereditary and Environmental Factors in the Pathogenesis of Rheumatic Fever. E. F. Diamond.—p. 908.
The Rheumatic Child and His World: An Ecologic Speculation. I. Galdston.—p. 916.
Rabies Prophylaxis in Man. K. Habel.—p. 923.
Education: The Adolescent and Pediatric Education. J. R. Gallagher.—p. 937.
Massive Resection of the Small Intestine in the Neonatal Period: Report of Two Successful Cases and Review of the Literature. G. P. Pilling and S. L. Cresson.—p. 940.
Neurologic Diseases in Infancy and Childhood: Summary of Seminar. W. A. Hawke and J. S. Prichard.—p. 949.
Use of Adrenal Hormones in Treatment: Summary of Round Table Discussion. A. M. Bongiovanni and W. R. Eberlein.—p. 958.
Clinical Conference: Cystinosis. N. Kretchmer.—p. 962.

The Maintenance Need for Water in Parenteral Fluid Therapy.—A system for the calculation of maintenance fluid needs for children of all ages on the basis of energy expenditure is proposed. Calories are calculated according to the following formulae, based on weight of the patient: (1) 0 to 10 kg., 100 Cal. per kilogram; (2) 10 to 20 kg., 1000 Cal.+50 Cal. per kilogram for each kilogram over 10 kg.; (3) 20 kg. and up, 1500 Cal.+20 Cal. for each kilogram over 20 kg. These relationships are designed to yield values which are intermediate in expenditure between normal activity and basal requirements. A comparison of figures obtained by this system with those obtained by other recognized systems is presented.

A fluid requirement of 100 ml. per 100 Cal. is proposed, and the justification for this in terms of insensible loss and urinary requirements is discussed. There is also a discussion of the requirements for electrolytes in maintenance therapy and values of sodium (3.0), potassium (2.0), and chloride (2.0) per 100 Cal. are advised. Reasons for the choice of these figures are also presented.

News and Comment

ANNOUNCEMENTS

Refresher Course in Pediatrics.—A refresher course in pediatrics will be conducted at St. Christopher's Hospital for Children, Philadelphia, by the Pediatric Department of Temple University School of Medicine on May 21 to 24, 1958. Each half-day session will be devoted to a single phase of pediatric medicine. For information regarding enrollment, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia 33.

Sister Elizabeth Kenny Foundation Scholarships.—The Sister Elizabeth Kenny Foundation announces a continuance of its postdoctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of neuromuscular diseases.

Kenny Foundation Scholars will be appointed annually. Each grant provides a stipend of from $5000 to $7000 a year for a five-year period, depending upon the Scholar's qualifications. Candidates from medical schools in the United States and Canada are eligible.

Inquiries concerning details should be sent without delay to Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, 2400 Foshay Tower, Minneapolis 2.

International Society of Hematology.—The Seventh Congress of the International Society of Hematology will be held in Rome at the Palazzo dei Congressi, EUR, on Sept. 7 to 13, 1958. The official languages of the Congress will be English, French, German, Italian and Spanish.

Preliminary program: (1) immunohematology; (2) hemorrhagic disorders; (3) leukemia; (4) anemia; (5) nucleonics; (6) the spleen and the reticuloendothelial system.

For further information please write to: Segreteria del VII Congresso Internazionale di Ematologia, Istituto di Patologia Medica, Policlinico Umberto I, Roma, Italia.

The Congress of the International Society of Blood Transfusions will be held at the same Palazzo dei Congressi on Sept. 3 to 6.

Postdoctoral Fellowships in Research and Clinical Allergy.—The American Foundation for Allergic Diseases announces the availability of postdoctoral fellowships in research and clinical allergy, each to extend for two years.

Stipend: first year, $4500; second year, $4750; laboratory and travel expenses for two-year period, $750.

Requirements: Candidates must be graduates of approved medical schools and must have completed one or two years of the graduate training required as a preliminary to certification by the Boards of Internal Medicine or Pediatrics; they are to divide their time between research and clinical training, and in the second year 10% or 15% of a candidate's time might be devoted to teaching. The respective institutions have taken the necessary steps to have this training credited toward the Sub-specialty in Allergy by the Board of Internal Medicine and the Board of Pediatrics.

Requests for applications should be sent directly to one of the following, in whose field the candidate would like to work: Dr. Colin M. MacLeod, Professor of Research Medicine, University of Pennsylvania, 820 Maloney Clinic, 36th and Spruce Streets, Philadelphia 4, or Dr. Herman N. Eisen, Professor of Medicine (Dermatology), Washington University School of Medicine, 600 South Kingshighway, Saint Louis 10. Applications should be filed no later than Dec. 15, 1957, with either of the above. Notification will be mailed to successful candidates by Feb. 1, 1958.

Benjamin Knox Rachford Lectures.—The twenty-sixth annual series of the Benjamin Knox Rachford Lectureships will take place in Cincinnati on Tuesday and Wednesday evenings, Feb. 11 and 12, 1958, at 8:30 p.m. Dr. Robert A. Good, American Legion Memorial Heart Research Professor of Pediatrics at the University of Minnesota, will deliver these

lectures in the auditorium of the Children's Hospital Clinic and Research Building. On Feb. 11 Dr. Good will lecture on "Disturbances in Agammaglobulinemia and Antibody Synthesis," and on Feb. 12 the subject will be "Diffuse Renal Diseases in Childhood."

Third-Year Residency in Pediatric Specialties.—St. Christopher's Hospital for Children, Department of Pediatrics, and Temple University School of Medicine, Philadelphia, are offering a special residency providing longitudinal experiences in several of the subspecialties of pediatrics throughout the year, available to candidates who have had an internship and two years of pediatric residency.

The resident may participate in the planning of his program. One or more days of each week may be spent in such specialties as cardiology, neurology, hematology, endocrinology, allergy, and psychiatry.

This program has been devised as a pilot study for the training of pediatricians to fill the gap now existing between the general practitioner type of pediatrician and the one highly skilled in a given specialty. It is thought that pediatricians with such additional training should (1) improve materially the quality of general pediatric practice, (2) serve more adequately as consultants with the general practitioner, and (3) work effectively with the larger pediatric centers in the care of children who for one reason or another must receive a part of their medical care in such centers.

Appointments will be made for residencies beginning on July 1, 1958, about March 1, 1958.

For applications write to Waldo E. Nelson, M.D., St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia 33.

GENERAL NEWS

Philadelphia Association for Blind, New Children's Leaflets.—The Philadelphia Association for the Blind announces the publication of three new leaflets particularly pointed toward the care of children's eyes: "Cross-Eyes," "Check Your Child's Eyes," and "What's the Score on Your Infants' Eyes?" These leaflets have been designed to complement a complete program in the greater Philadelphia Area during September, October, and November themed to the slogan of "Regular Eye Examination Today—Healthy Eyes for Tomorrow." Parents are especially urged during these months to have their children's eyes examined regularly, and they are cautioned to watch for these six warning danger signs in their children's eyes: cross eyes; headaches and nervousness; red, watery, itchy eyes; rubs eyes often; squints when looking at objects; holds head to one side. Persons and organizations wishing sample copies of these leaflets may write to Philadelphia Association for the Blind, 100 E. Price St., Philadelphia 44, Attn: Prevention of Blindness Department.

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., in Chicago, Oct. 11, 12, and 13, 1957.

Alberti, Aurora Frances, Somerset-Chevy Chase, Md.
Bacon, John Louis, Rockford, Ill.
Beem, Marc Oliver, Chicago.
Bilder, Joseph, Jr., Denison, Texas.
Blizzard, Robert Martin, Columbus, Ohio.
Bussey, Dan R., Pompano Beach, Fla.
Byrum, Robert Jordan, Davenport, Iowa.
Cleveland, Robert W., Long Beach, Calif.
Cole, Wyman, C. C., Jr., Detroit.
Conway, Thomas J., Terre Haute, Ind.
Davis, David William, Chanute AFB, Ill.
Deatrick, Richard Wallace, Ann Arbor, Mich.
Dew, Philip E., Tucson, Ariz.
Doblin, Morton Joseph, Skokie, Ill.
Dochios, Mary, Chicago.
Eisenberg, Bernard, Williamsville, N. Y.
Fernbach, Donald J., Houston, Texas.
Foxworthy, John Paul, East Grand Rapids, Mich.
Freeman, William S., Beloit, Wis.
Gagliardi, Carl A., Dearborn, Mich.
Gallen, William Joseph, Milwaukee.
Gamble, William B., Jr., Charleston, S. C.
Goldberg, Marvin H., Sherman Oaks, Calif.
Green, Clayton Robbie, Excelsior, Minn.
Haddy, Theresa Brey, Arlington Heights, Ill.
Harmuth, Arthur M., Pittsburgh.
Harris, Jack Kenneth, Louisville.
Hellerstein, Stanley, Kansas City, Kan.
Herz, Janice Greenberg, Chicago.
Hildebrandt, H. Mark, Ann Arbor, Mich.
Hofmann, Adele D., Englewood, N. J.
Holman, Gerald Hall, Baltimore.
Holve, Leslie M., Los Angeles.
Hubbard, Edwin C., Walpole, Mass.
Keith, L. E., Chicago.
Kohlenbrener, Robert M., Skokie, Ill.
Kruger, Leon E., Newton Centre, Mass.
Lassers, Elisabeth S., Chicago.

Lavrich, James Howard, Euclid, Ohio.
Leventer, Ira, Detroit.
Levin, Jerry Charles, Chicago.
Levin-Epstein, Ralph Henry, Holyoke, Mass.
Link, Etta C., Berkley, Mich.
Hirschmann-Lutwak, Asna, Chicago.
Mandel, Samuel, New York.
Manson, Gordon, Detroit.
Mebane, Donald Cummins, Toledo, Ohio.
Mendelsohn, Robert Saul, Chicago.
Metrick, Seymour, Chicago.
Miles, James Verner, Jr., Jamestown, N. D.
Mosier, Harry David, Jr., Los Angeles.
Mosser, Robert Schaaf, Glen Burnie, Md.
Nyhan, William L., Jr., Lombard, Ill.
Pearlman, Julian L., Lexington, Mass.
Pinkerton, Herman H., Jr., Abingdon, Va.
Plotkin, Robert Frederick, Broomall, Pa.
Ratajik, Alyda Rene, Oak Lawn, Ill.
Richardson, George B., Cleveland Heights, Ohio.
Roads, Wesley A., Fairborn, Ohio.
Roos, Richard K., Boulder, Colo.
Schnabel, Robert Frederick, Crookston, Minn.
Schubert, William Kuenneth, Cincinnati.
Scott, Carl Hartford, Lexington, Ky.
Shapiro, Robert Everett, Syracuse, N. Y.
Shea, Daniel Wright, Green Bay, Wis.
Sherard, Earl S., Jr., Columbus, Ohio.
Sissman, Norman Joseph, Baltimore.
Smith, Lowell D., Chillicothe, Ohio.
Sosin, Allen, Farmington, Mich.
Starkman, Morris, Detroit.
Stephens, Raymond N., Mansfield, Ohio.
Stirlacci, Joseph R., Springfield, Mass.
Sullivan, Mary Catherine, Westchester, Ill.
Szandra, Joseph, Chicago.
Swarts, Charles Louis, Chicago.
Thompson, David I., Carlisle, Pa.
Turnauer, Elisabeth Friedl, New York.
Wachtel, Philip L., Freeport, N. Y.
Wadlington, William B., Donelson, Tenn.
Waite, Malcolm Edward, Rochester, N. Y.
Wegner, Kurt J., Youngstown, Ohio.
Weinberg, Herbert L., Suffolk, Va.
Weiner, Frieda M., Chicago.
Werner, Stanley G., Aurora, Ill.
Wilkinson, Robert H., Boise, Idaho.
Winokur, Paul Arthur, Cranford, N. J
Winters, Robert Wayne, Chapel Hill, N. C.
Witt, Governor, Palm Beach, Fla.
Zolliker, Margaret, St. Clair Shores, Mich.

Special Foreign Certificates

Herdocia Lacayo, Filiberto, León, Nicaragua, Central America.
Kilic, Nizamettin, New York.
Valyasevi, Aree, Philadelphia.

PERSONAL

Dr. Harris D. Riley Jr.—Dr. Harris D. Riley Jr. has resigned his position in the Department of Pediatrics at Vanderbilt School of Medicine to accept the position of Professor of Pediatrics and Chairman of the Department of Pediatrics at the University of Oklahoma School of Medicine, Oklahoma City. He will leave soon to assume his new duties. In addition to being an instructor in the Department of Pediatrics, Dr. Riley was Assistant Medical Director of the Poliomyelitis Respiratory Center at Vanderbilt Hospital.

Riley was graduated from Vanderbilt School of Medicine in 1948. He served his internship at Baltimore City Hospitals and Johns Hopkins. After residency training at Babies and Children's Hospital, Western Reserve University in Cleveland, he returned to Vanderbilt to complete his residency in pediatrics. After some two years of service in the U. S. Air Force Medical Service, he returned to Vanderbilt on a fellowship in Pediatrics and was appointed to his present position.

Directory of Pediatric Societies*

INTERNATIONAL

Ninth International Congress of Paediatrics

President: Dr. Allan Ross, 1615 Cedar Ave., Montreal, Canada.
Place: Montreal. Time: 1959.

International Union for Child Welfare

Chairman of Executive Committee: Judge M. Ch. de Jong, 10 Hogeweg, Wassenaar, Netherlands.
Secretary General: Dr. Georges Thelin, 1 Rue de Varembe, Geneva, Switzerland.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. J. D. Bailey, 140 Brown's Line.
Secretary: Dr. John A. MacLean, 51 Eglinton Ave. East.
Place: Academy of Medicine. Meetings: Once a month.

Asociacion de Pediatrías Españoles

President: Dr. Rafael Ramos Fernández.
Vice-Presidents: Dr. Juan Bosch Marín and Dr. Ciriaco Laguna.
Secretary-General: Dr. Luis Navas Migueloa.
Treasurer: Dr. Angel Ballabriga.

Australian Paediatric Association

President: Dr. T. Y. Nelson, 235 Macquarie St., Sydney, N. S. W.
Vice-President: Dr. Kate Campbell, 33 Collins St., Melbourne, Victoria.
Secretary: Dr. S. P. Bellmaine, 141 Macquarie St., Sydney, N. S. W.
Treasurer: Dr. D. L. Day, 137 Macquarie St., Sydney, N. S. W.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Prof. F. M. B. Allen.
Secretary: Dr. P. R. Evans, Hospital for Sick Children, Great Ormond St., London, W. C. 1.

Canadian Paediatric Society

President: Dr. J. Harry Ebbs, 555 University Avenue, Toronto 2.
Secretary-Treasurer: Dr. J. C. Rathbun, 526 Waterloo St., London, Ont.

Clinical Pediatric Society of Israel

Chairman: Dr. I. Heyman, Hadassah Municipal Hospital, Tel Aviv.
Committee: Dr. E. Schoenfeld, Tsahalon Government Hospital, Jaffa, Tel Aviv; Dr. Bernard E. Cohen, Tel Hashomer Government Hospital, Tel Litwinski.
Place: Hospital Pediatric Services throughout country. Time: Bi-monthly.

Danish Pediatric Society

Chairman: Dr. Poul W. Braestrup, County Hospital of Copenhagen, Hellerup.
Vice-Chairman: Dr. Jorgen Vesterdal, The State Hospital, Blegdamsvej, Copenhagen.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Secretary: Dr. Harald Kreutzfeldt, The National Health Service, Slotsholmsgade 10, Copenhagen.
Place: A Children's Hospital in Copenhagen. Time: Wednesday, as a rule once a month.

Deusche Gesellschaft für Kinderheilkunde

President: Prof. Dr. med. W. Keller, Universitäts-Kinderklinik, Freiburg/Brsg.
President-Elect: Prof. Dr. med. K. Klinke, Kinderklinik d. Medizinischen Akademie, Moorenstr. 5, Dusseldorf.
Secretary: Prof. Dr. med. J. Jochims, Städt. Kinderklinik, Kronsforder Allee 71/73, Lübeck.

Finnish Paediatric Association

President: Dr. Niilo Hallman, Children's Hospital, 11 Stenback St., Helsinki-Toolo.
Secretary: Dr. Kalle Osterlund, Children's Hospital, 11 Stenback St., Helsinki-Toolo.

Greek Pediatric Association

President: Dr. Spiros Bartsocas.
Honorary Secretary: Dr. Egle Inglessi, 4 Milioni St., Athens.

Israel Pediatric Society

Chairman: Prof. Sh. Rosenbaum, 26 Bialik St., Tel Aviv.
Secretary: Dr. R. Kochmann, 131 Ben Jehuda Rd., Tel Aviv.
Place: Tel Aviv.

Nederlandse Vereeniging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerink, c/o Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Norsk Pediatrisk Selskap

President: Dr. Henrik Hagelstein, Children's Department, Rikshospitalet, Oslo.
Secretary: Dr. Kare Havard Torp, Children's Department, Ullevål Hospital, Oslo.
Time: Friday, six times a year.

Paediatric Society of New Zealand

President: Dr. S. L. Ludbrook, Lister Bldg., Victoria Street East, Auckland C. 1.
Vice-President: Dr. Murray McGeorge, Medical School, Dunedin.
Honorary Secretary: Dr. R. H. Caughey, 58 Symonds St., Auckland C. 1.
Honorary Treasurer: Dr. Alice M. Bush, 18 Symonds St., Auckland C. 1.
Place: Dunedin. Time: August.

Paediatric Society of Victoria

President: Dr. J. F. Williams, 12 Collins St., Melbourne.
Honorary Secretary: Dr. H. E. Williams, Royal Children's Hospital, Carlton.
Place: Lecture Theatre of the Royal Children's Hospital.
Time: Second Wednesday in each month at 8:00 p. m.

Philippine Pediatric Society

President: Dr. Florencio N. Quintos.
Secretary-Treasurer: Dr. Lino. Ed. Lim, Manila.
Place: Physician's Club, Dewey Blvd., Manila. Time: Every two months; last Thursday of September, November, January, and March.

Royal Society of Medicine, Section of Paediatrics

President: G. H. Macnab, F.R.C.S.
Honorary Secretaries: Ursala James, M.R.C.P., and Leslie Scott, M.D.
Sectional Editor: D. MacCarthy, M.D.
Place: 1 Wimpole St., London W.1 (correspondence for these honorary officers should be sent to this address). Time: Fourth Friday of each month, 4:15 p. m.

SCHWEIZERISCHE GESELLSCHAFT FÜR PÄDIATRIE

President: Prof. W. Tobler, Brunnadernrain 11, Bern.
Vice-President: Prof. M. Jaccottet, Av. de Rumine, Lausanne.
Secretary: Dr. J. Haas, Westl. Alpenstrasse 3, Burddorf.

SOCIEDAD ARGENTINA DE PEDIATRÍA

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

SOCIEDAD BOLIVIANA DE PEDIATRÍA

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

SOCIEDAD CHIHUAHUENESE DE PEDIATRÍA

President: Dr. Alfonso Riuz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., Mexico.

SOCIEDAD CHILENA DE PEDIATRÍA

President: Prof. Dr. Raúl Gantes A.
Secretary-General: Dr. Edmundo Cardemil.
Place: Medical Society, Merced 565, Santiago.

SOCIEDAD COLOMBIANA DE PEDIATRÍA

President: Dr. Alfonso Vargas Rubiano.
Vice-President: Dr. Darío Gutiérrez Laserna.
Secretary: Dr. Omar García Bustamante.
Treasurer: Dr. Alfonso Gutiérrez Reyes.

SOCIEDAD CUBANA DE PEDIATRÍA (FILIAL CIENFUEGOS)

President: Dr. Rafael Viego Delgado.
Secretary: Dr. Ramón Azaret Morón, Santa Cruz No. 167, Cienfuegos, Cuba.
Place: Colegio Médico. Time: 9:00 p. m., Wednesdays, six times a year.

SOCIEDAD ECUATORIANA DE PEDIATRÍA

President: Dr. Aldo Muggia.
Secretary: Dr. Nicolas Espinosa, Hospital Baca Ortiz, Quito, Ecuador, S. A.
Place: Hospital Baca Ortiz, Quito, Ecuador. Time: Monthly.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Daniel Campos, Hospital Clínico Regional, Concepción.
Secretary: Dr. Obdulia Jiménez, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month, April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DEL LITORAL

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary-General: Dr. Elsa Galimany.

SOCIEDAD DE PEDIATRÍA DEL ATLANTICO

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Treasurer: Dr. Hernando Barrios-Angulo.

SOCIEDAD URUGUAYA DE PEDIATRÍA

President: Dr. Euclides Peluffo.
Secretary: Dr. Rubin Gorlero Bacigalupi.
Place: Av. Agraciada 1464, piso 13, Montevideo.

Sociedad Venezolana de Puericultura y Pediatría

President: Dr. Miguel Raga.
Vice-President: Dr. Jorge Lizarraga.
Secretary: Dr. Hernan Mendez C.

Sociedad Yucateca de Pediatría

President: Dr. Humberto Perez Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

Sociedade Meneira de Pediatría

President: Dr. Agostinho Fernandes.
Secretary: Dr. Celio Marques Scotti.

Sociedade de Pediatria da Bahia

President: Dr. Elysio Pereira de Atbayde.
Secretary: Dr. Eliezer Audiface.

Sociedade de Pediatria de Pernambuco

President: Dr. Antonio Aureliano.
Secretary: Dr. Claudia Figueiredo.

Sociedade de Pediatria do Rio Grande do Sul

President: Dr. Francisco Talaia de Moura.
Secretary: Dr. Enio Pilla.

Sociedade Portugesa de Pediatria

President: Prof. Dr. Lucio de Almeida.
Vice-President: Dr. Cordeiro Ferreira.
Secretary-General: Prof. Dr. Carlos Salazar de Sousa.
Treasurer: Dr. Mario Cordeiro.
Place: Clinica pediatrica do Hospital D. Estefania, Lisbon. Time: Monthly.

Sociedade de Puericultura e Pediatria do Maranbao

President: Dr. Ordorico Amaral de Mattos.
Secretary: Dr. Joao Mohana.

Société de Pédiatrie de Montréal

President: Dr. Rémi Archambault.
Vice-President: Dr. Claude Leonard.
Secretary: Dr. Paul Dagenais-Perusse, La Société de Pédiatrie de Montréal, Inc.

Société de pédiatrie de Paris

President: Prof. Marcel Lelong, 197 Boulevard St-Germain (VII).
Secretary: Prof. Maurice Lamy, 94 Rue de Varenne (VII).
Place: Hôpital des enfants-malades, 149 Rue de Sevres (XV). Time: 4:00 p. m., third Thursday of each month.

Société de Pédiatrie de Québec

President: Dr. Roland Thibaudeau, 203 des Erables.
Secretary: Dr. Euclide Dechêne, 312 du Roi.
Place: Quebec. Time: May and November.

Societa Italiana di Pediatria

President: Prof. Giuseppe Caronia.
Vice-Presidents: Prof. Mario Cotellessa and Prof. Gaetano Salvioli.
Secretary: Prof. Rolando Bulgarelli.

South African Paediatric Association

Chairman: Dr. H. L. Wallace, Durban.
Honorary Secretary-Treasurer: Dr. F. Walt, 126 Trust Building, Gardiner St., Durban.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. Sture Siwe, Lund.
Secretary: Dr. Karl-Axel Melin, Färjestadsvägen 16, Bromma.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Docent Justus, Ström, Stockholm.
Secretary: Dr. M. d'Avignon, Pediatric Clinic, Karolinska Sjukhuset, Stockholm 60.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm. Time: Second Friday of each month, except summer.

UNITED STATES

National

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edgar E. Martmer, 693 Washington Rd., Grosse Pointe 30, Mich.
Vice-President and President Elect: Dr. Stewart H. Clifford, 1101 Beacon St., Brookline 46, Mass.
Executive Secretary and Treasurer: Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill.

AMERICAN MEDICAL ASSOCIATION, SECTION ON PEDIATRICS

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee.
Secretary: Dr. Wyman C. C. Cole, 3001 W. Grand Blvd., Detroit 2.

AMERICAN PEDIATRIC SOCIETY

President: Dr. A. Ashley Weech.
Vice-President: Dr. Alton Goldbloom.
Secretary-Treasurer: Dr. Aims C. McGuinness, Room 1036, 2800 Quebec St., N. W., Washington 8, D. C.
Meetings: Hotel Traymore, Atlantic City, N. J., May 8, 1958. The Inn, Buck Hill Falls, Pa., June 15, 1959.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Edward Pratt
Vice-President: Dr. Alexander Nadas
Secretary-Treasurer: Dr. Sydney S. Gellis, 818 Harrison Ave., Boston 18.
Meeting: May 6 and 7, 1958. Place: Hotel Traymore, Atlantic City, N. J.

Sectional

INTERMOUNTAIN PEDIATRICS SOCIETY

President: Dr. Stanley Childs, 2000 So. 9th East, Salt Lake City.
Vice-President: Dr. Hal Wakefield, Utah Valley Hospital, Provo, Utah.
Secretary: Dr. Robert S. Ely, 1940 So. 2nd East, Salt Lake City.
Place: Salt Lake City.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Edward T. Wakeman, 240 Bradley St., New Haven, Conn.
President-Elect: Dr. Allan M. Butler, Mass. General Hospital, Boston 14.
Secretary: Dr. Harry Shwachman, Childrens Hospital, Boston.
Place: Boston for three meetings and one in another Northeast city. Time: October, December, March, and June.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. Gorham Babson, 1107 S. W. 13th, Portland 5, Ore.
President-Elect: Dr. Norman Murphy, Seattle.
Secretary: Dr. Peter Spohn, 3195 Granville St., Vancouver, B. C.
Meeting: April, Seattle.

Northern Ohio Pediatric Society

President: Dr. C. W. Wyckoff.
President-Elect: Dr. William M. Champion.
Secretary-Treasurer: Dr. James B. Stewart, Babies and Childrens Hospital, 2103 Adelbert Rd., Cleveland 6.

Northwestern Pediatric Society

President: Dr. Elizabeth G. Lowry, 301 Kenwood Parkway, Minneapolis.
Vice-President: Dr. C. O. Kohlbry, 226 North 1st Ave., Duluth, Minn.
Secretary-Treasurer: Dr. John J. Galligan, 868 Lowry Bldg., St. Paul.

Rocky Mountain Pediatric Society

President: Dr. James Kennedy, 1447 Florence, Denver.
Vice-President: Dr. Leo J. Flax, 1575 Vine, Denver 6.
Secretary-Treasurer: Dr. Jules Amer, 1575 Vine, Denver 6.
Place: University Club, Denver.

Southwestern Pediatric Society

President: Dr. Thomas Harris, 436 N. Roxbury Drive, Beverly Hills, Calif.
Vice-President: Dr. Wendell Redfern, 125 E. Glenoaks Blvd., Glendale, Calif.
Secretary: Dr. Gordon Richardson, 10711 Riverside Drive, North Hollywood, Calif.
Place: University Club, Los Angeles. Time: September, November, January, and March.

Western Society for Pediatric Research

President: Dr. James F. Bosma, 1940 So. 2nd East, Salt Lake City.
Vice-President: Dr. William Deamer, Dept. of Pediatrics, University of California, San Francisco.
Secretary: Dr. Robert H. Alway, Stanford School of Medicine, San Francisco.
Place: Salt Lake City.

State

Alabama State Pediatric Society

President: Dr. Daniel W. Burke, 1452 Springhill Ave., Mobile.
Vice-President: Dr. Thomas C. Nolan, 803 Adams Ave., Montgomery.
Secretary-Treasurer: Dr. John F. Shriner, 1916 Government St., Mobile.
Place: Montgomery.

Arizona State Pediatric Society

President: Dr. B. P. Starts, 1018 N. Country Club Rd., Tucson.
Secretary: Dr. Jack H. Demlow, 130 S. Scott, Tuscon.
Time: Spring and Fall.

California Medical Association, Section on Pediatrics

Chairman: Dr. Moses Grossman, University of California Medical Center, San Francisco.
Secretary: Sidney Rosin, 6230 Wilshire Blvd., Los Angeles.

Florida State Pediatric Society

President: Dr. Wesley S. Nock, 273 Alhambra Circle, Coral Gables.
Vice-President: Dr. Joel V. McCall Jr., 111 Broadway, Daytona Beach.
Secretary-Treasurer: Dr. Henry G. Morton, 1950 Arlington Ave., Sarasota.

Georgia Pediatric Society

President: Dr. Frank Thomas, Albany.
Vice-President: Dr. Bessie Mae Beach, 309 Martin Bldg., Columbus.
Secretary: Dr. C. Dixon Fowler, 27 Eighth St., N. E., Atlanta.
Time: May.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. James M. Sturtevant, 358 Montauk Ave., New London.
Treasurer: Dr. Edward T. Wakeman, 240 Bradly St., New Haven.
Secretary: Dr. Robert P. Rogers, 90 Dayton Ave., Greenwich.

Illinois State Medical Society, Section on Pediatrics

Chairman: Noel G. Shaw, 636 Church St., Evanston.
Secretary: Raymond Eveloff, 1025 South 7th St., Springfield.

Indiana State Pediatric Society

President: Dr. Byron K. Rust, 3740 Central Ave., Indianapolis 5.
Secretary: Dr. Wallace E. Bash, 2318 S. Fairfield Ave., Ft. Wayne 6.

Iowa Pediatric Society

President: Dr. Maryelda Rockwell, 220 Tucker Bldg., Clinton.
Vice-President: Dr. Harold E. Farnsworth, 612½ Lake Ave., Storm Lake.
Secretary: Dr. Ralph E. Dyson, 3200 University Ave., Des Moines 11.
Place: Spring meeting in conjunction with the Iowa State Medical Society meeting; fall meeting in September at University Hospital, Iowa City.

Kansas State Pediatric Society

President: Dr. David R. Davis, Emporia.
Vice-President: Dr. C. T. Hinshaw, Wichita.
Secretary: Dr. Theodore Young, 103½ East Ninth St., Winfield.
Place: Broadview Hotel, Emporia.

Kentucky Pediatric Society

President: Dr. Alexander J. Alexander, 109 Esplanade, Lexington.
Secretary: Dr. Robert B. Warfield, 180 Market Street, Lexington.
Place: Lexington. Time: Spring, 1957.

Louisiana State Pediatric Society

President: Dr. Suzanne Schaefer, 3439 Prytania St., New Orleans.
Vice-President: Dr. Conway S. Magee, Gordon Bldg., Lake Charles.
Secretary: Dr. Joseph M. Perret, Jr., 2329 S. Carrollton, New Orleans.
Place: New Orleans. Time: Spring, 1957.

Michigan State Medical Society, Pediatric Section

President: Dr. Harry A. Towsley, University Hospital, 1313 Ann St., Ann Arbor.
Secretary: Dr. Charles Frank Payton, 611 S. Washington, Royal Oak.

Montana Pediatric Society

President: Dr. George W. Nelson, Billings.
Vice-President: Dr. Joseph W. Brinkley, Great Falls.
Secretary: Dr. Frank J. Friden, Great Falls.
Time: Twice yearly, usually March and September.

Nebraska Pediatric Society

President: Dr. E. S. Wegner, 724 Sharp Bldg., Lincoln.
Vice-President: Dr. Robert Grant, 909 Sharp Bldg., Lincoln.
Secretary: Dr. Gilbert Schreiner, 125 No. 38th St., Omaha.
Place: Omaha. Time: Third Thursday of each month at the Childrens Memorial Hospital, Omaha.

New Hampshire Pediatric Society

President: Dr. Arthur Laidlaw, Keen.
Secretary-Treasurer: Dr. Robert F. Wilson, 113 Locust St., Dover.
Place: Concord, Manchester, Dover, Hanover.

New Mexico Pediatric Society

President: Dr. Albert S. Lathrop, P. O. Box 912, Coronado Bldg., Santa Fe.
Vice-President: Dr. Guy E. Rader, 4120 Silver S. E., Albuquerque.
Secretary: Dr. Carol K. Smith, P. O. Box 2056, Coronado Bldg., Santa Fe.
Place: Variable. Time: Four times a year.

North Carolina Pediatric Society

President: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.
Vice-President: Dr. George A. Watson, 306 S. Gregson St., Durham.
Secretary: Dr. Bailey Webb, 809 W. Chapel Hill St., Durham.

South Carolina Pediatric Society

President: Dr. William R. Deloache, 13 Medical Court, Greenville.
Vice-President: Dr. Fred F. Adams, 157 Pine St., Spartanburg.
Secretary: Dr. Guy C. Castles Jr., 1417 Gregg St., Columbia.

Tennessee Pediatric Society

President: Dr. Thomas Fort Bridges, 1814 Hayes St., Nashville.
Vice-President: Dr. William G. Crook, 648 W. Forest St., Jackson.
Secretary: Dr. Stewart Smith, 605 Lindsay St., Chattanooga 3.
Place: Nashville.

Texas Pediatric Society

President: Dr. Russell J. Blattner, Baylor Medical College, Houston.
President-Elect: Dr. E. M. Wier, 1216 Pennsylvania, Forth Worth.
Secretary: Dr. James N. Walker, 5216 W. Freeway, Forth Worth.

Virginia Pediatric Society

President: Dr. T. S. Chalkley, 3011 Monument Ave., Richmond.
Vice-President: Dr. A. P. Booker, 1021 West Main St., Charlottesville.
Secretary-Treasurer: Dr. Harry L. Cox, 113 Fauquier St., Portsmouth.
Place: Williamsburg.

Wisconsin State Medical Society, Section of Pediatrics

Chairman: Dr. E. H. Pawsat, Fond du Lac.
Vice-Chairman: Dr. Samuel E. Kohn, Milwaukee.
Secretary: Dr. J. R. Schroder, Janesville.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave. (12).
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave. (6).
Place: Allen Memorial Medical Library. Time 8:15 p. m., October, December, February, and March.

Akron Pediatric Society

President: Dr. Lewis E. Rector, 410 Akron Savings and Loan Bldg.
Vice-President: Dr. Noah Miller, 193 West Market St.
Secretary: Dr. Walter W. Lang, 154 N. Water St., Kent, Ohio.

Baltimore City Medical Society, Pediatric Section

President: Dr. Melchijah Spragins, 102 Alleghany Ave., Towson 4, Md.
Vice-President: Dr. Harry H. Gordon, Sinai Hospital of Baltimore, Inc., Monument St. and Rutland Ave. (5).
Secretary: Dr. B. M Debuskey, 2501 W. Belvedere Ave.
Place: 1211 Cathedral St. Time: Second Tuesday in November, January, and March at 8:30 p. m.

Baton Rouge Pediatric Society

President: Dr. Cecil O. Dorio, Roumain Bldg.
Vice-President: Dr. Clifton T. Morris, Roumain Bldg.
Secretary-Treasurer: Dr. Stephen L. Madey, 1401 N. Foster Drive.
Place: Variable. Time: Quarterly as called.

Bronx Pediatric Society

President: Dr. Harold Aaron, 647 W. 207 St., New York.
Vice-President: Dr. Jess Diamond, 1900 Grand Concourse, New York.
Secretary-Treasurer: Dr. Archie Cohn, 2280 Grand Ave., New York.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August, and September.

Brooklyn Academy of Pediatrics

President: Dr. J. Philip Lombard, 115 Woodruff Ave. (26).
Vice-President: Dr. Adolph H. Emerson, 7721 Ridge Blvd. (9).
Secretary-Treasurer: Dr. Morris Steiner, 456 E. 19th St. (26).
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October, and November.

Buffalo Pediatric Society

President: Dr. Norman C. Bender, 227 Colvin Ave.
Vice-President: Dr. Thomas S. Bumbalo, 354 Lincoln Parkway.
Secretary-Treasurer: Dr. Lois J. Plummer, 131 Linwood Ave.

Central Illinois Pediatric Society

President: Dr. O. E. Ehrhardt, 1321 S. 4th St., Springfield.
President-Elect: Dr. Howard R. Miller, 114 Statford Drive, Peoria.
Secretary-Treasurer: Dr. Richard E. Dukes, Carle Hospital Clinic, Urbana.
Time: April and October.

Central New York Pediatric Club

President: Dr. Paul W. Beaven, 20 N. Goodman St., Rochester.
Vice-President: Dr. Howard A. Gilmartin, Schenectady.
Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester.
Time: Twice Yearly.

Central Ohio Pediatric Society

President: Dr. Miner W. Seymour, 375 E. Town St., Columbus.
Secretary: Dr. William E. Baldock, 4150 Indianola Ave., Columbus.

Chicago Pediatric Society

President: Dr. Ralph H. Kunstadter, 664 N. Michigan Ave. (11).
Vice-President: Dr. Noel G. Shaw, 636 Church St., Evanston, Ill.
Secretary: Dr. Raymond F. Grissom, 715 Lake St., Oak Park, Ill.
Treasurer: Dr. Philip L. Aries, 3952 W. Jackson Blvd. (24).

Cincinnati Pediatric Society

President: Dr. William D. De Vaux, 7373 Brookcrest Dr.
Vice-President: Dr. Daniel V. Jones, 7373 Brookcrest Dr.
Secretary: Dr. Harold A. Cassady, 2728 Erie Ave.
Place: Research Library, Children's Hospital. Time: On call.

Cleveland Academy of Medicine, Pediatric Section

Chairman: Dr. Robert Hauver, 10515 Carnegie Ave.
Secretary: Dr. William Herman, 10300 Carnegie Ave.

Corpus Christi Pediatric Society

President: Dr. Jack F. McKemie, 527 Gordon.
Vice-President: Dr. Hannah B. Woody, 515 Elizabeth.
Secretary: Dr. Jos. Oshman, 1010 Ohio.

Dallas Pediatric Society

President: Dr. Floyd A. Norman, 4325 Cole Ave.
Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave.
Place: Children's Hospital of Texas. Time: 6:30 p. m., first Thursday in each month.

Des Moines Pediatric Society

President: Dr. Arnold M. Smythe, 923 Bankers Trust Bldg.
Vice-President: Dr. Charles L. Burr, 5701 Hickman Rd.
Secretary-Treasurer: Dr. Everett A. Nitzke, 520 39th St.
Place: Des Moines Golf and Country Club. Time: Fourth Tuesday of each month from September to May.

Detroit Pediatric Society

President: Dr. Glen E. Hause, 18520 Grand River (23).
President-Elect: Dr. Louis E. Heideman, 20211 Greenfield (35).
Secretary: Dr. Charles G. Jennings, 14827 E. Jefferson. (14).
Treasurer: Dr. Douglas Wake, 1307 S. Washington, Royal Oak, Mich.
Permanent Mailing Address: 5224 St. Antoine (2).

Forth Worth Pediatric Society

President: Dr. Randall Nyman, 1015 Pennsylvania.
Secretary: Dr. James Hooher, 1111 Pennsylvania.
Place: Variable. Time 6:30 p. m., third Friday of each month.

Hinterland Pediatric Society

President: Dr. Arthur Varden, 755 E. Gilbert St., San Bernardino, Calif.
Vice-President: Dr. John Wilcox, 150 Nemaha Rd., Pomona, Calif.
Secretary-Treasurer: Dr. George A. Chalfant, 124 E. F St., Ontario, Calif.
Place: Alternating between Riverside, San Bernardino, and Pomona, Calif. Time: February May, September, and November.

Honolulu Pediatric Society

President: Dr. Douglas Murray.
Secretary: Dr. Duke Cho Choy, 1010 S. King St.
Place: Homes of members. Time: Third Thursday of each month.

Houston Pediatric Society

President: Dr. R. E. Leaton, 3012 San Jacinto.
Vice-President: Dr. M. Eleanor Blish, 4705 Montrose.
Secretary: Dr. Elizabeth Bratteng, 1729 Sunset.
Place: Announced. Time: Fourth Tuesday of January, March, May, July, September, and November.

Kansas City Southwest Pediatric Society

President: Dr. Frank Houge, Plaza Medical Bldg., Kansas City, Mo.
Secretary: Dr. S. J. Kranson, Truman Rd. and Ash, Independence, Mo.
Place: University Club, Kansas City, Mo. Time: On call.

Long Beach Pediatric Society

President: Dr. Kenneth Berkaw, 211 Cherry Ave.
Secretary: Dr. C. W. Latshaw, 3821 Atlantic Ave.
Place: Victor Hugo Restaurant, 730 E. Broadway. Time: First Tuesday night of every month.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Margaret H. Jones.
Vice-President: Dr. Wendell M. Redfern.
Secretary-Treasurer: Dr. Morris J. Naiditch, 239 S. La Cienega Blvd., Beverly Hills, Calif.

LOUISVILLE PEDIATRIC SOCIETY

President: Dr. Selby V. Love, 108 Cannons Lane (6).
Secretary: Dr. Patrick Hess, New Albany, Ind.
Place: Variable. Time: Five times a year.

MEDICAL SOCIETY OF THE COUNTY OF KINGS, BROOKLYN, PEDIATRIC SECTION

President: Dr. Arthur L. Ruby.
Vice-President: Dr. David Dragutsky.
Secretary: Dr. Abraham Gilner, 303 Beverly Rd. Brooklyn 18.
Treasurer: Dr. Saul Starr.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Vice-President: Dr. Wm. A. Howard, 1517 30th St. N. W., Washington, D. C.
Secretary: Dr. John E. Cassidy, 9911 Old Georgetown Rd., Bethesda, Md.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. Price Stepp, 848 Adams.
Vice-President: Dr. W. R. Graves, 505 South Highland.
Secretary: Dr. Robert G. Jordan, 848 Adams.
Place: Rotated among four hospitals. Time: 7:30 p. m., second Tuesday each month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. Vernon Kores, 6040 W. Lisbon Ave.
Vice-President: Dr. Karl Beck, 1411 Wauwautosa Ave.
Secretary: Dr. Paul S. Pierson, 1513 E. Capitol Drive.
Place: University Club. Time: Quarterly.

MOBILE PEDIATRIC SOCIETY

President: Dr. Daniel Sullivan, 1420 Government St., Mobile, Ala.
Secretary: Dr. Robert O. Harris III, 1514 Government St., Mobile Ala.
Place: Admiral Semmes Hotel. Time: 7:30 p. m., fourth Thursday of September, November, January, March, and May.

MONTGOMERY COUNTY PEDIATRIC SOCIETY

President: Dr. Harris P. Dawson, 45 Adams Ave., Montgomery, Ala.
Vice-President: Dr. William R. Britton, 133 S. Union, Montgomery.
Secretary-Treasurer: Dr. Thomas C. Nolan, 803 Adams Ave., Montgomery.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. Ethel Walker 2509 West End Avenue, Nashville 5, Tenn.
Secretary: Dr. Richard P. Taber, 2801 Gallatin Rd., Nashville 6, Tenn.
Place: Homes of members. Time: Third Thursday of each month.

NASSAU PEDIATRIC SOCIETY

President: Dr. Virginia Lent, 285 N. Franklin St., Hempstead, N. Y.
Vice-President: Dr. Selma Buchbinder, 295 Harvard Ave., Rockville Centre, N. Y.
Secretary-Treasurer: Dr. David Posner, 98 Wolcott Rd., Levittown, N. Y.
Place: Felice's Restaurant, Westbury, Long Island. Time: 7:30 p. m., second Monday evening in February, April, June, October, and December.

NEW ORLEANS PEDIATRIC SOCIETY

President: Dr. Joseph M. Perret Jr., 2329 S. Carrollton Ave.
Vice-President: Dr. James L. Treadway, 4325 Clara St.
Secretary: Dr. G. J. Fruthaler.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Benjamin Kramer, 60 Plaza St., Brooklyn.
Secretary: Dr. Henry L. Barnett, 535 East 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St., New York.
Time: 8:30 p. m., every second Thursday of October through May.

Northern California Pediatric Society

President: Dr. E. Revere Cole, 2901 Capitol Ave., Sacramento 16.
Vice-President: Dr. Hubert Long, 2320 Channing Way, Berkeley 4.
Secretary: Dr. Samuel Hurwitz, 6200 Geary Blvd., San Francisco 21.
Place: St. Francis Hotel, San Francisco. Time: Quarterly as called.

Northern Ohio Pediatric Society

President: Dr. Chauncey W. Wyckoff.
President-Elect: Dr. William M. Champion.
Secretary-Treasurer: Dr. James B. Stewart, Babies and Childrens Hospital, 2103 Adelbert Rd., Cleveland.

Oklahoma City Pediatric Society

President: Dr. Charles L. Freed, 430 N. W. 12th St.
Secretary: Dr. Jerome D. Shaffer, 1200 North Walker.
Place: Varies. Time: On Call.

Philadelphia Pediatric Society

President: Dr. Elizabeth Kirk Rose, 426 Owen Rd., Wynnewood, Pa.
Secretary: Dr. Robert H. High, 316 Simms St. (16).
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. W. W. Briant Jr., 633 Washington Rd.
Vice-President: Dr. R. R. Macdonald, 448 Brownsville Rd.
Secretary: Dr. B. I. Michaels, 3500 5th Ave.
Place: Varies. Time: October, December, February, and April.

Queens Pediatric Society

President: Dr. Abram S. Tepper, 1225 Beach 12th St., Far Rockaway, N. Y.
Secretary: Dr. Emanuel Fletcher, 140-10 Franklin Ave., Flushing 55, N. Y.
Place: The Seminole Club, 112th St. and 70th Rd., Forest Hills, N. Y. Time: Second Tuesday of October, December, February, and April.

Richmond Pediatric Society

President: Dr. Hobart T. Dougan, 1832 Monument Ave., Richmond 20, Va.
Secretary: Dr. Robert A. Hoffman, 1001 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July, and August.

St. Louis Pediatric Society

President: Dr. Alfred S. Schwartz.
Vice-President: Dr. James P. King.
Secretary: Dr. Mirriam H. M. Pennoyer, 500 S. Kingshighway Blvd.
Place: Medart's Restaurant. Time: 7 p. m., second Thursday of each month from September to May, inclusive.

San Antonio Pediatric Society

President: Dr. Virginia Stovall, South Texas Building, San Antonio, Texas.
Vice-President: Dr. Ben Shaver, Medical Arts Building, San Antonio.
Secretary: Dr. C. Scott Stewart, 123 Ogden Lane, San Antonio.
Place: Bexar County Medical Library. Time: 7:00 p. m., first Tuesday of each month.

Santa Barbara Pediatric Society

President: Dr. Clarence B. Hills, 22B. W. Micheltorena St., Santa Barbara, Calif.
Secretary: Dr. Louise P. Brown, 3017 Foothill Rd., Santa Barbara.
Place: Varies. Time: Two to three times yearly, on call.

Seattle Pediatric Society

President: Dr. O. William Anderson.
President-Elect: Dr. Robert Tidwell.
Secretary-Treasurer: Dr. James L. Tucker.
Place: College Club. Time: 6:30 p. m., fourth Friday of each month from September to June.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Robert Trimby, Lansing, Mich.
Secretary: Dr. George H. Lowrey, University Hospital, Ann Arbor, Mich.
Place: University Hospital, Ann Arbor. Time: Yearly as announced.

Waco Pediatric Society

President: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Secretary: Dr. A. O. Manske.
Place: 1918 Austin Ave., Waco. Time: Third Tuesday of each month.

Westchester County Medical Society, Pediatric Section

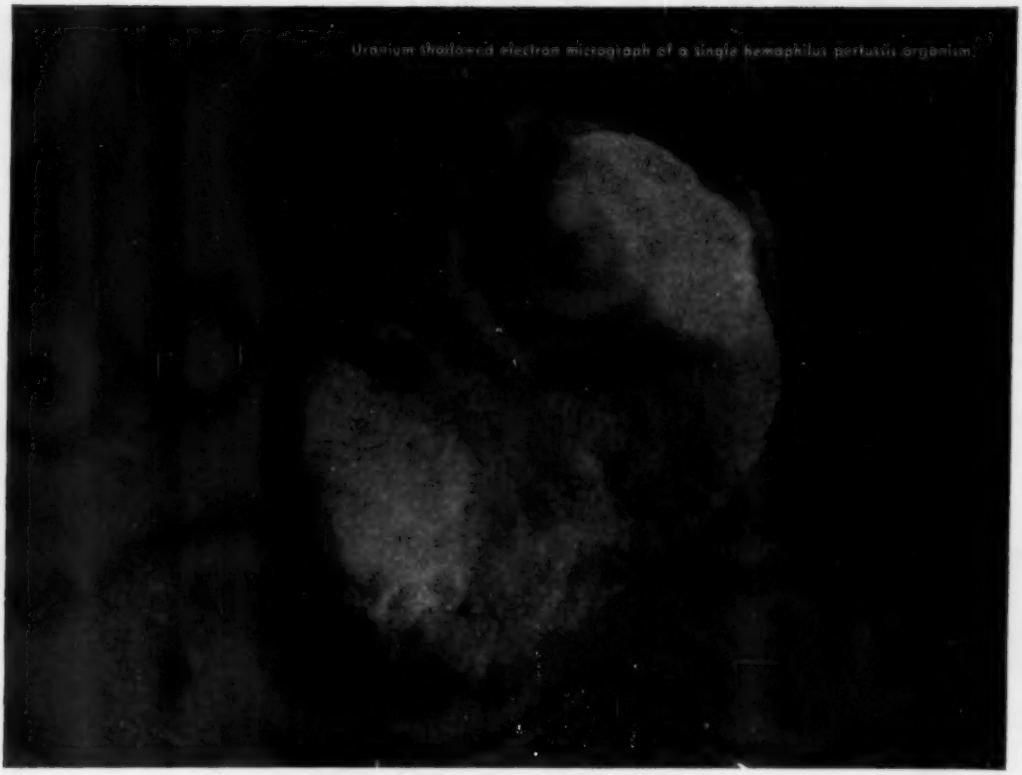
Chairman: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Secretary: Dr. Irving Nelson, 150 E. Hartsdale Ave., Hartsdale, N. Y.
Place: Various hotels and clubs in the County. Time: Four meetings yearly—November, February, April, and June.

Western Michigan Pediatrics Society

President: Dr. John W. Thompson, 833 Lake Drive, S. E., Grand Rapids.
Vice-President: Dr. Ethon L. Stone, 721 17th St., Jackson.
Secretary: Dr. Donald C. Johns, 655 Broadview S. E., Grand Rapids.
Place: Grand Rapids in November and March. Other west Michigan cities in September and June.

Wichita Pediatric Society

President: Dr. Wm. F. McGuire.
Secretary: Dr. Katherine Pennington, Sedgwick County Medical Society, Schwiter Building, Wichita, Kan.
Place: Homes of members. Time: 8:30 p. m., first Thursday, October through May.



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Longmire, Jordan and Briggs; Ann. Surg. 144: 681, 1956

Krane; Am. Pract. and Digest, 8: 1273, 1957

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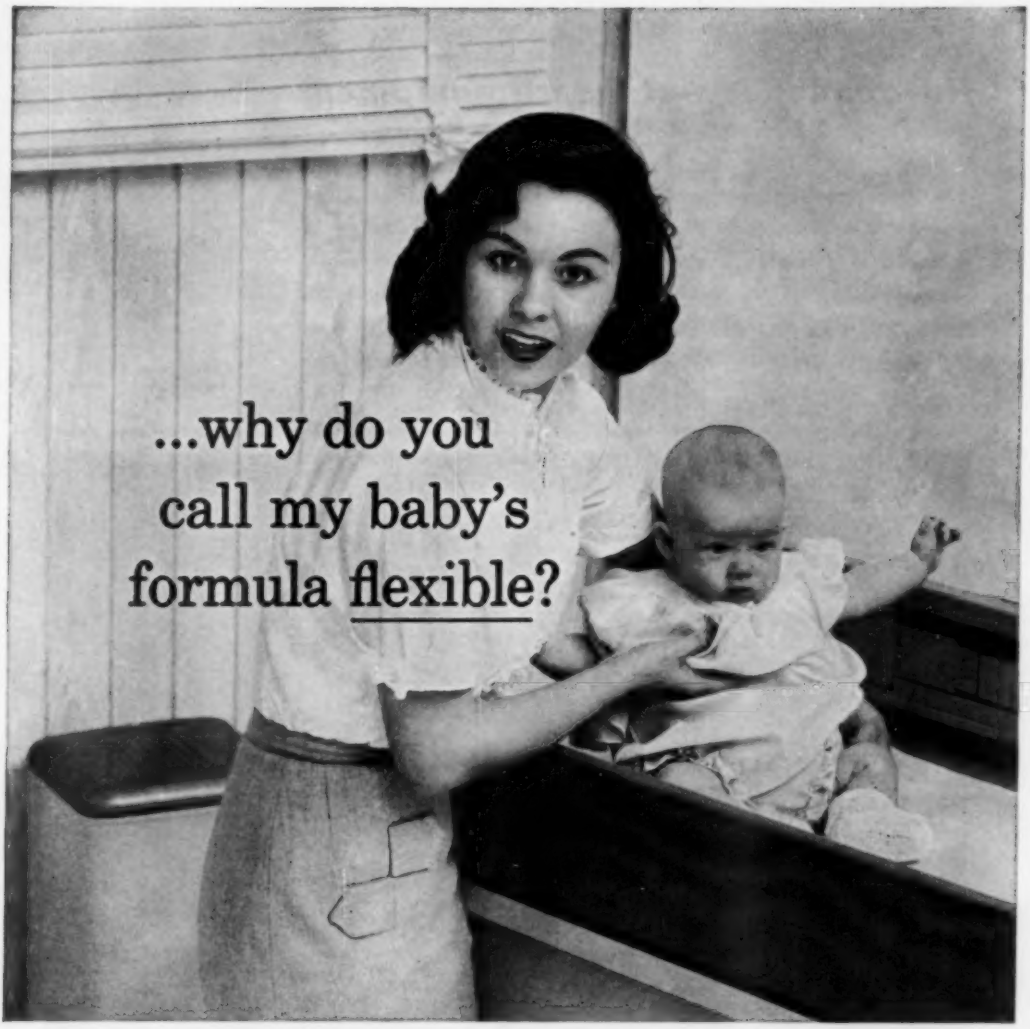

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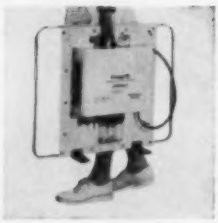

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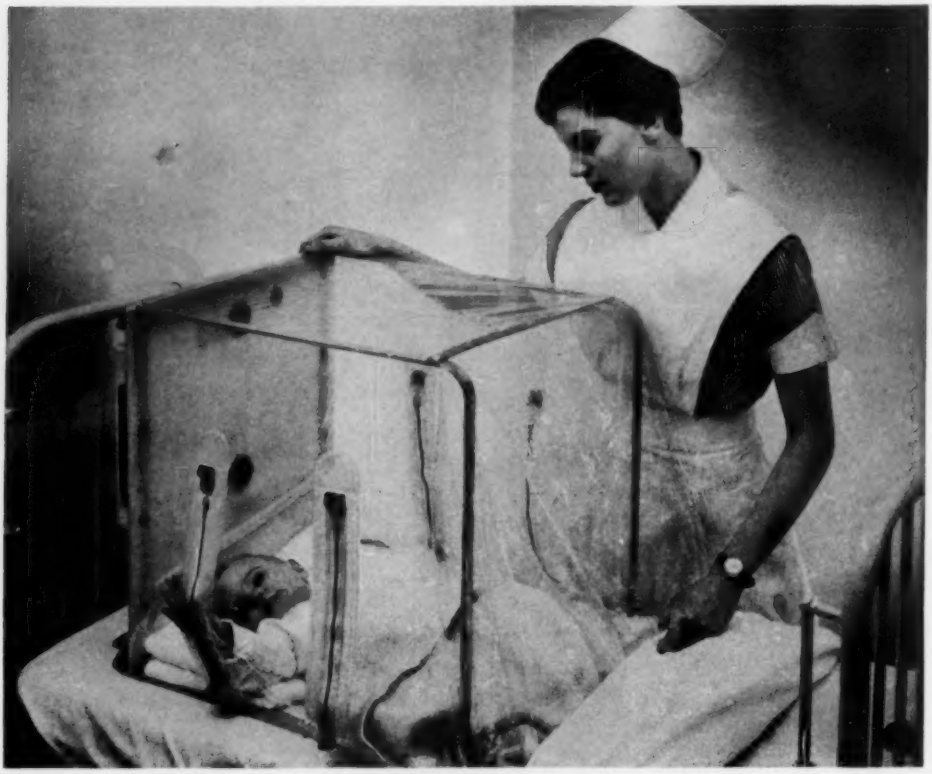

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